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PAROXYSMAL AND PERSISTENT HYPERTENSION IN ASSOCIATION WITH LESIONS OF THE ADRENAL GLANDS

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IN THE attempt to unravel the enigma of hypertension it has become apparent that the adrenal glands, in some instances at least, are implicated. Between the opinion of Goldzieher that the adrenals are altered in practically all instances of hypertension and are fundamentally concerned with its course, and the opinion of those who hold, on the contrary, that the adrenals are little or not at all concerned, there is now established a middle ground. The relation of hyperplasia of the cortex and of tumors of both the cortex and the medulla of the adrenal gland to paroxysmal and also sustained hypertension is now definitely proved, and both Goldzieher and Bauer give specific instances in which hyperplasia of the medulla has been held responsible for hypertension. Furthermore, the experimental work of Goldblatt[1] has shown that hypertension fails to occur in dogs whose renal arteries have been compressed with metal clamps if the adrenal cortices have been previously removed, and subsides in dogs with well-established hypertension whose adrenal cortices are later removed.

In establishing the relationship of the adrenal glands to hypertension, the reporting of instances in which this relationship has been proved by post-mortem examination or by surgical intervention has, to date, been of first importance. This paper summarizes such of these clinical instances as we have been able to find in the medical literature. To these instances we have added two of our own. The first is unlike other reported cases in that marked hyperplasia of the adrenal cortex and a cortical adenoma were apparently responsible for the development of hypertension in spite of the presence of definite cardiac decompensation. The second is an instance in which the symptoms at first simulated angina pectoris, but a diagnosis of medullary adrenal

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tumor was later made, and confirmed by operation; the successful removal of the tumor resulted in permanent relief of symptoms, including the paroxysmal hypertension.

Oppenheimer and Fishberg,[2] in reporting an instance of hypertension due to cortical adrenal hyperplasia, gathered the previous cases of this kind from the literature, beginning with Edmund Neusser's observation, in 1898, of two patients who ran a clinical course of nephritis with hypertension. At necropsy, the kidneys and arteries were found to be normal. There was in each instance a neoplasm of the suprarenal gland, described as a carcinoma. Vaquez (1904) demonstrated that diffuse hyperplasia and circumscribed adenoma formation in the suprarenal cortex were frequently found in hypertensive individuals. Aubertin and Ambard (1904) reported four instances of diffuse cortical hyperplasia associated with hypertension, and three of cortical adenoma. Bland-Sutton (1918) recorded an instance of tumor of the suprarenal cortex in which there was an enormous cardiac hypertrophy for which no other cause could be found. Mackintosh (1920) recorded an instance of a 14-year-old boy with obesity, hirsuties of the forehead, eyebrows, chin, axilla, and pubis, and striae atrophicae on the abdomen. The blood pressure was 240/170. The left lower ribs bulged. The author considered this an instance of suprarenal hyperplasia. Hoag (1923) published an instance of a 4-year-old girl with precocious sexual development. The blood pressure ranged from 160/100 to 145/90. A hypernephroma was revealed at autopsy, associated with arteriosclerosis of the pial vessels.

In Table I the recorded instances of hypertension that are attributed to hyperplasia or tumor of the adrenal cortex are listed.

Our Case 1 differs from any of these in that a woman, 62 years old, whose blood pressure had been low for many years (90/60) began, in the face of very evident cardiac decompensation, to develop an increased pressure. It rose gradually over a period of one month to 180/100, and maintained this level uniformly for four months. During this period marked anasarca was continuously present. The patient died of congestive heart failure. The possible causes of this persistent increase in pressure during the course of very evident cardiac decompensation were basophilic adenoma of the pituitary gland, or hyperplasia or tumor of the adrenal gland. A roentgenogram of the sella demonstrated no enlargement. Cushing's syndrome was not evident in this patient. A slowly growing epithelioma near the right labium, which had twice been removed, suggested the possibility of a metastatic malignant growth in one of the adrenal glands.

REPORT OF CASE

CASE 1.—*History:* A woman, aged 62, was examined in February, 1934. The complaints were fatigue and anorexia for six months; a small tumor in the right side of the vulva; intermittent swelling of the ankles and face toward evening, absent

the following morning, for three months; and shortness of breath during the night requiring many pillows, for six weeks. Previous illnesses included typhoid fever at the age of 24 years and influenza at 60. Early in 1930 she noted a lump in the right labium, which grew slowly until it was the size of an egg. It caused little discomfort but occasioned some disagreeable discharge. On July 14, 1931, after a few days of fever and of swelling in the right groin, a gland was drained and part of the tumor removed. The diagnosis on this tissue was basal cell carcinoma. The wound healed promptly. No postoperative radiation was given. In January, 1932, the lump had returned. Biopsy of this tissue was reported as showing "malignant characteristics." At this time weekly subcutaneous injections of a "cancer cure serum" were given. In February, 1933, a vaginal growth was removed by electrocautery. The wound healed promptly. The "cancer cure serum" was continued. There followed periods of physical overwork and attempts to reduce the weight (212 pounds) which she had maintained for many years.

General Examination.—Height 5 feet, 6 inches; weight 206 pounds. The bony frame was large. The face was of hexagonal shape. Adipose tissue was abundant but rather uniformly distributed over the entire body. The skin had an alabaster tint; it was very dry. The outer third of the eyebrows was thin. The hair of the scalp was rather thin, fine in texture, and dry. There was little or no hair over the torso and extremities. There was moderate pitting edema of the hands, fingers and ankles. The sclerae showed a slight icteric tint.

The heart was hypertrophied; in the orthodiagram the transverse diameter was 15.3 cm., with a chest width of 24.0 cm. The width of the great vessels was 5.0 cm. The rate was 80 per minute, with normal rhythm. There was a soft systolic murmur in the second right intercostal space which was transmitted to the great vessels. The blood pressure was 100/60.

Fine moist râles were present at the base of each lung. Roentgenograms showed that there were increased bronchial markings about the right hilum. The lung fields were otherwise clear. The left side of the diaphragm was level with the right; they moved equally.

The edge of the liver was felt on deep inspiration; it was firm, smooth, and not tender.

There was an extensive scar about the vulva and high in the vagina on the right. There was a more suspicious, harder, pea-sized mass just beneath the scar, an inch inside the vagina. There was an indurated area on the right vulva which measured 1 by 0.5 cm.

Laboratory Examinations.—The urine showed a trace of albumin, with 15 to 20 leucocytes to a microscopic field. There was a hypochromic anemia; the hemoglobin was 75 per cent, the erythrocyte count 3,670,000, the color index 1, the leucocyte count 5,900, and the differential leucocyte count normal. The blood Wassermann reaction was negative. The blood sedimentation rate was within normal limits. The basal metabolic rate was minus 29 per cent. The electrocardiogram gave evidence of left ventricular preponderance.

Course.—The patient was followed for a period of six months, until the time of her death, July, 1934. Repeated blood pressure determinations during February gave no reading higher than 115 systolic, 60 diastolic. During March the pressure rose steadily until in the latter part of the month a reading of 180/100 was obtained. The pressure was maintained at this level until shortly before death. Edema became more and more marked, until general anasarca was present. Digitalization and diuretics did not lessen the edema. The heart rate varied from 70 to 104.

Blood chemical studies, which at first had shown nothing abnormal, gave the following results in July: nonprotein nitrogen 167.8 mg. per 100 c.c.; uric acid

12.2 mg. per cent; creatinine 5.7 mg. per cent; sugar 156 mg. per cent; cholesterol (whole blood) 176 mg. per cent. These values remained essentially unchanged until the end.

The nodule on the right labium grew slowly, reaching a maximum size of 3 by 1 cm. No evidence of metastases on physical examination or on repeated roentgenologic examinations was obtained.

The urine just before death contained large amounts of albumin and hyaline, granular and renal failure casts.

Autopsy.—One thousand cubic centimeters of bloodstained yellow fluid were collected from the abdominal cavity, and it was estimated that another 300 c.c. escaped measurement. The free edge of the liver was the width of three fingers below the costal margin. There were collected from the pleural cavities 1,350 c.c. of blood stained fluid. The pericardial fluid amounted to 50 c.c. and was slightly cloudy.

The heart weighed 520 gm. The pericardial surface was dull and was covered with a thin layer of fibrin. The maximum thickness of the wall of the left ventricle was 2 cm., and that of the right, 1 cm. The coronary orifices were patent, the walls thin. The lining of the aorta was smooth throughout. The remainder of the gross observations are not pertinent to this report.

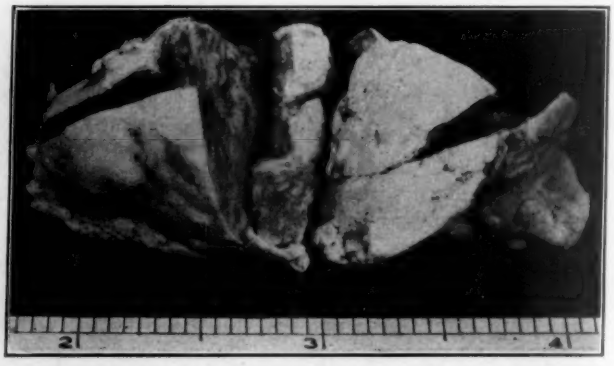

Fig. 1.—Tumor right adrenal cortex, at autopsy. Case 1.

The right adrenal gland weighed 27 gm. and measured 6 by 3.5 by 2.5 cm. Surfaces made by cutting were soft in consistency and yellow in color. The left adrenal weighed 10 gm. and measured 5 by 3 by 0.6 cm.

The left kidney weighed 141 gm. Its capsule stripped with ease. The surface was slightly granular. On surfaces made by cutting, the cortex was 5 mm. in thickness and pale. In several regions it was sharply demarcated from the medullary pyramids, which were beefy red. The lining of the pelvis was smooth, gray, and glistening. The right kidney weighed 125 gm. Surfaces made by cutting were similar to the left kidney.

The liver weighed 2,090 gm. Its surface was smooth and firm. Surfaces made by cutting were about 20 per cent yellow with fat and had a nutmeg appearance. The spleen weighed 360 gm. The parenchyma was firm and slate-purple in color.

The pancreas and the thyroid were normal and weighed, respectively, 150 and 19 gm.

The uterus and ovaries were small, but of normal proportion. There was a slightly raised red-brown nodule in the middle of the right labium majus, 2 cm. in diameter and elevated about 5 mm.

Permission for examination of the brain was refused.

Anatomic Diagnoses.—Marked generalized hypertrophy and dilatation of the heart; fibrinous pericarditis; marked anasarca; hypostatic hyperemia and edema of the lungs; passive hyperemia of the liver; cyanotic induration of the spleen; adrenal cortical hyperplasia; cortical adenoma; tumor nodule of the right labium majus; obesity.

Histologic Examination.—There was a uniform and diffuse hyperplasia of the entire cortex of the left adrenal, its average width being 3.5 mm. On sectioning the entire gland, adenomas were not found. There was a marked hyperplasia of the entire cortex of the right adrenal. In addition, there was a large nodule in the cortex, poorly demarcated. It measured 4 by 2 cm. On gross section it appeared histologically of the same structure as the cortex itself. The cells of the cortex of the right gland were arranged in a compact alveolar fashion. The nuclei appeared somewhat smaller than those of the opposite adrenal and the cytoplasm was somewhat more vacuolated. There was no evidence of any medullary elements.

In the kidneys there was moderate thickening of the walls of the medium-sized blood vessels. The capsules of Bowman were not thickened. There were no other unusual findings in the kidneys. The changes in the liver and spleen were consistent with chronic passive congestion. In the heart muscle the fibers were moderately widened. There was no scarring. In the pancreas and in the thyroid there was nothing abnormal.

In sections of the ovary there were numerous scars. The blood vessels were thickened, many of them to a point of occlusion. A few small follicular cysts were seen. There was no sign of malignancy.

COMMENT

Our report differs from any of those in the literature in that a woman, 62 years old, whose blood pressure had been low for some years (90/60 to 110/60), began in the face of very evident cardiac decompensation to develop an increased pressure. It rose gradually over a period of a month to 180/100 and maintained this level uniformly for 4 months, i.e., until a few days before her death from congestive failure. During this period anasarca was continuously present.

The possible causes of this persistent increase in pressure during the course of evident decompensation were: (1) basophilic adenoma of the pituitary gland, (2) tumor of the adrenal gland, or (3) hyperplasia of the adrenal cortex or medulla. A roentgenogram of the sella turcica demonstrated no enlargement. Cushing's syndrome was not evident in this patient. A slowly growing epithelioma in the right labium, which had been twice removed, suggested the possibility of a malignant metastatic growth in one of the adrenals. The absence of metastases in connection with this malignant lesion was attested by the autopsy examination.

Our second presentation is an instance of pheochromocytoma. The diagnosis was made before operation, and there has been complete disappearance of the symptoms since the tumor was removed a year ago.

To date, there have been approximately eighty-five instances of pheochromocytoma reported in the literature. In only twenty was a

clinical diagnosis made. Undoubtedly, a considerable number of these tumors are masquerading under a variety of symptoms and so escaping detection. Clinicians of the future, however, will be enabled to make more clear-cut diagnoses through roentgenologic studies preceded by the injection of air about the adrenal glands, after the method first described by Carelli and modified by Cahill, Loeb, et al.,[3] of New York City. In many instances, this will also eliminate the necessity of an exploratory incision on one side in the hope that the suspected tumor will lie on that side, and will determine whether or not there is an adequately functioning adrenal on the opposite side. Autopsies have shown that in 15 to 20 per cent of the cases the adrenal on the side opposite the tumor had functioned inadequately.

REPORT OF CASE

CASE 2.—*History:* This patient, a man, 56 years old, was first seen by us on July 27, 1936. His chief complaint was that he had been suffering from increasingly frequent "attacks" which were initiated by a feeling of dizziness, followed by nervousness and apprehension, a generalized headache, and palpitation of the heart. More recently there had been a pressure pain over the precordium which at times became intense and was then accompanied by marked shortness of breath. This pain did not radiate down the arm or up to the neck. The attacks usually occurred soon after he arose in the morning and before he had eaten anything. He stated that his wife could always predict the oncoming weak spell by his pallor, and that flushing of the skin became apparent as the symptoms subsided. During the subsidence he was conscious of tremor, weakness, fatigability. Usually the whole disturbance would last a relatively short time, from thirty seconds to fifteen minutes.

He was free of symptoms referable to the cardiorespiratory, gastrointestinal, or genitourinary system. His past history was negative, except for a severe streptococcus sore throat at the age of 45 years and erysipelas at the age of 50. His father died at the age of 81 of carcinoma of the stomach; his mother at the age of 42 years in childbirth. Three brothers died in childhood, and one sister at the age of 60 of some illness involving the nervous system. One sister was said to have had episodes similar to those of this patient, but had had no recurrence for some months.

General Examination.—Blood pressure 140/95; pulse rate 80; temperature normal. The chest was barrel-shaped, the expansion slightly limited. No evidence of fluid or congestion was found. The heart was not enlarged; the rhythm was normal, the sounds of good quality. An inconstant, blowing, untransmitted systolic murmur was heard at the apex. All of the peripheral arteries, including the dorsalis pedis, pulsated. The vessel walls seemed slightly thickened. The abdomen, genitalia, rectum, and extremities were negative.

Laboratory Examinations.—Kidney function tests showed slight impairment of the urea clearance (I C_u 47.0 per cent; 25.4 c.c. II C_u 46.3 per cent; 25.0 c.c.); normal excretion of phenolsulphonephthalein by ureteral catheterization; good concentration in the Volhard test on two occasions (specific gravity 1.006 to 1.030, and night volume 225 c.c.). A slight trace of albumin was noted on one occasion, but otherwise urinalyses were negative. The blood counts were normal. The icteric index was under nine. The blood Wassermann reaction was negative. The complexes of the electrocardiogram were essentially normal; there were occasional ventricular

extrasystoles. After an Ewald test meal the free hydrochloric acid was zero, the total acidity 11°. Basal metabolism determinations were not successful because of the early morning attacks suffered by the patient.

After the first examination the number of seizures for a time became much less and were mild in degree. When, for no reason that could be determined, the attacks again became more frequent and severe, the patient was hospitalized, March 18, 1937, and carefully studied for suspected adrenal disturbance. Attacks were at first initiated by carotid sinus pressure and the phenomena studied at will. Later, exercise before breakfast was sufficient stimulus to bring on an attack (Fig. 2). A relative bradycardia was noted in relation to the height of the blood pressure. During the attacks the heart sounds were loud. Many extrasystoles were present.

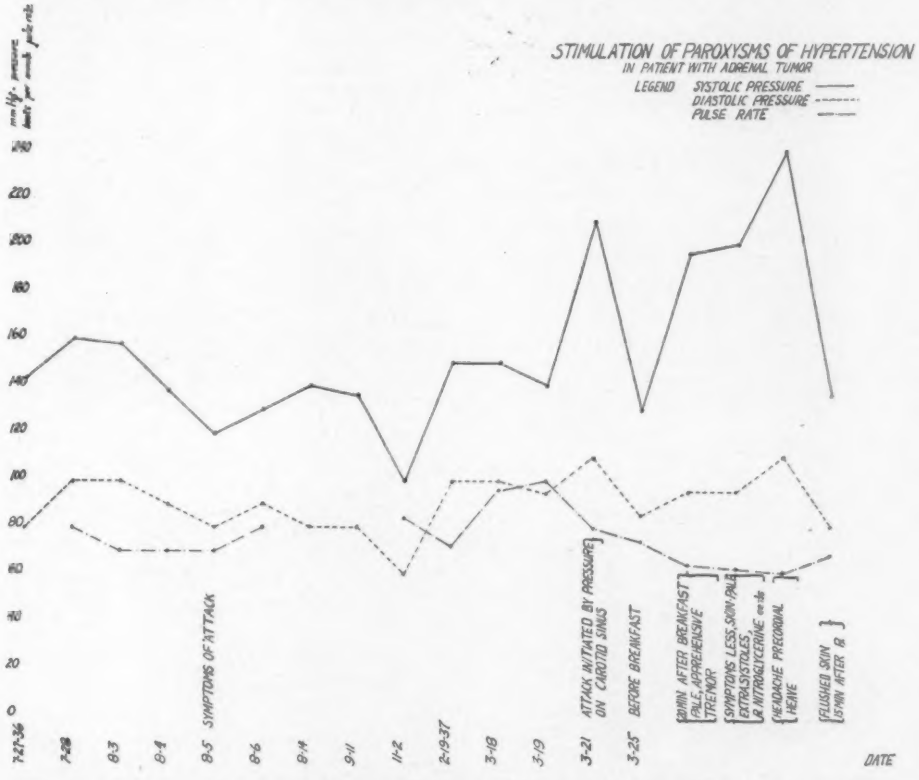

Fig. 2.—Episodes of hypertension induced by carotid sinus pressure and by exercise before breakfast.

The episodes of paroxysmal hypertension are illustrated in Fig. 3. These episodes occurred frequently, and it is probable that changes in the pressure were more abrupt than the records show. The attacks seemed to occur spontaneously. When the patient complained of dizziness, he would be quite pale and his extremities were cold and damp. He had an apprehensive expression, and complained of substernal pain and a feeling of shortness of breath and nausea. These symptoms would come and go as long as he remained pale. Later his face would flush and the symptoms would subside; this was followed by perspiration and a trembling of the hands and body.

Because of the vasomotor instability shown in the attacks and the variations in blood pressure, hyperadrenalinism was suspected. A glucose tolerance test revealed

mild intolerance (144, 166, 118, 88 mg. per 100 c.c. whole blood), which supported this belief. Gonadotropic hormone was not present in the urine. This test, as suggested by Frank,[4] should be made in all instances of suspected tumor of the adrenal glands. If an adrenal gland tumor is composed of cells of the adrenal cortex, the gonadotropic hormone will likely be present in the urine. Since it was absent in this instance, we felt that the tumor must be a pheochromocytoma, or less likely, that there was medullary hyperplasia. Goldzieher[5] cites four cases which he believes show significant relation between adrenal hyperfunction and hypertension. In each case one or more nodules were present, together with diffuse hyperplasia of the medulla. In two of the cases there was clinical evidence of hypertension. He be-

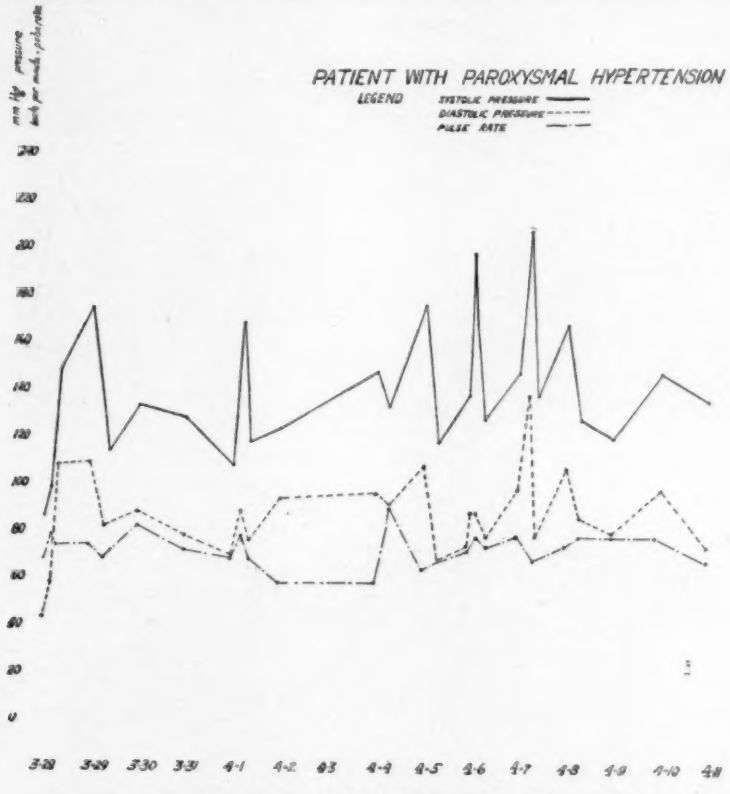

Fig. 3.—Episodes of paroxysmal hypertension induced by exercise.

lieves that the clinical manifestations of nodular hyperplasia do not differ essentially from those observed in cases of pheochrome tumors. Quantitative differences may exist and explain the rapid progress, paroxysmal character, and early fatal outcome in tumor cases, in contradistinction to the insidious onset, slow progress, and protracted course of hypertensive disease in the presence of nodular hyperplasia.

To further verify the diagnosis, perirenal air injection studies were made, after the method of Carelli as modified by Cahill et al.,[3] in conjunction with retrograde pyelography, and these studies revealed enlargement of the right adrenal shadow (Fig. 4).

With the diagnosis of a tumor of the right adrenal area thus established, an operation was performed by Dr. Samuel Robinson on April 12, 1937. When the adrenal gland was first manipulated during the course of the operative procedure, a paroxysm

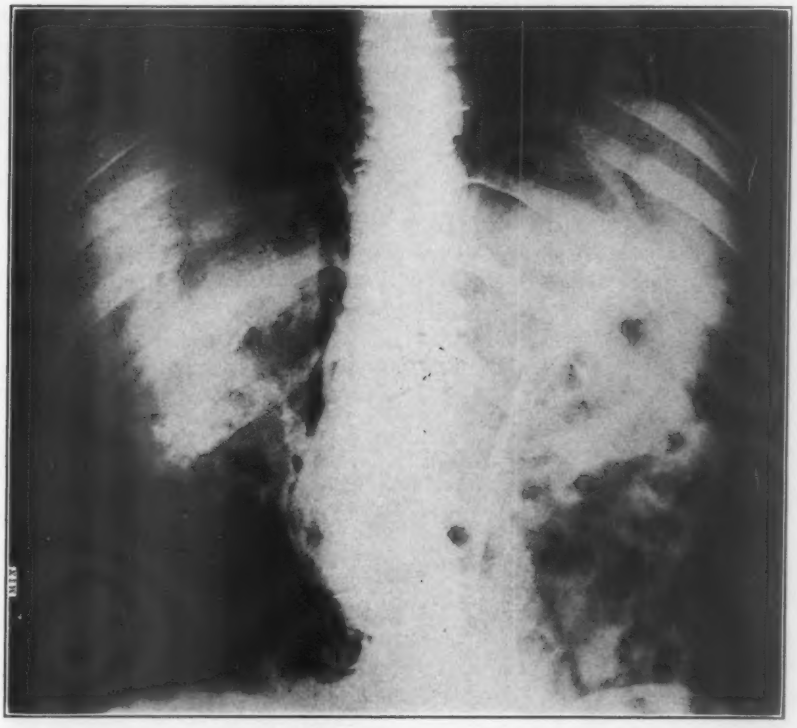

Fig. 4.—Perirenal air injections.

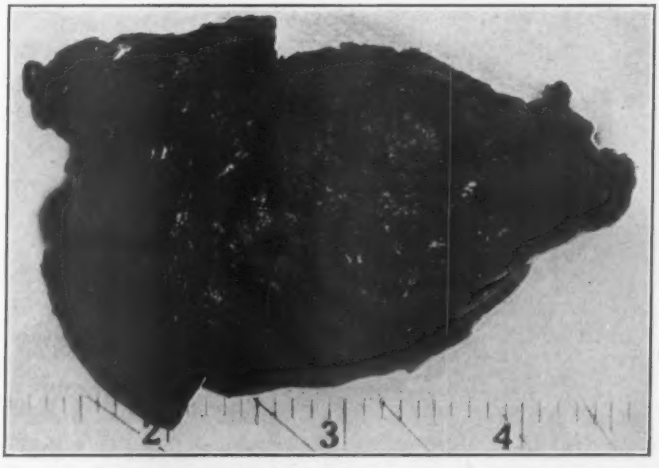

Fig. 5.—Right adrenal gland removed at operation. Case 2.

of hypertension was induced, the blood pressure rising suddenly from its usual level of 140/80 to 240/140. The paroxysm lasted approximately five minutes. Shortly after the adrenal gland and the tumor were removed the pressure dropped to a very low level (64/30). At this point in this operative procedure and for many hours thereafter hypoadrenalinism may exist, in which case proper therapeutic procedures should be instituted. Other readings made during that day were 98/50,

100/70, 96/80 (Fig. 6). The following day pressure readings higher than 112/74 were not obtained, but on the second day the pressure had returned to the preoperative level of 140/80.

The postoperative course was uneventful, and the patient was discharged from the hospital May 6, 1937. During the year that has elapsed since the operation there have been no recurrences of his former attacks, and the blood pressure has ranged from 120/80 to 140/80.

Pathologic Report.—The adrenal gland measured 3.5 by 2.3 by 2.2 cm. The midcavity was expanded by a gray-yellow, moderately firm mass of tissue which was bounded everywhere by a thin layer of yellow cortex 1 to 2 mm. thick. The cortex

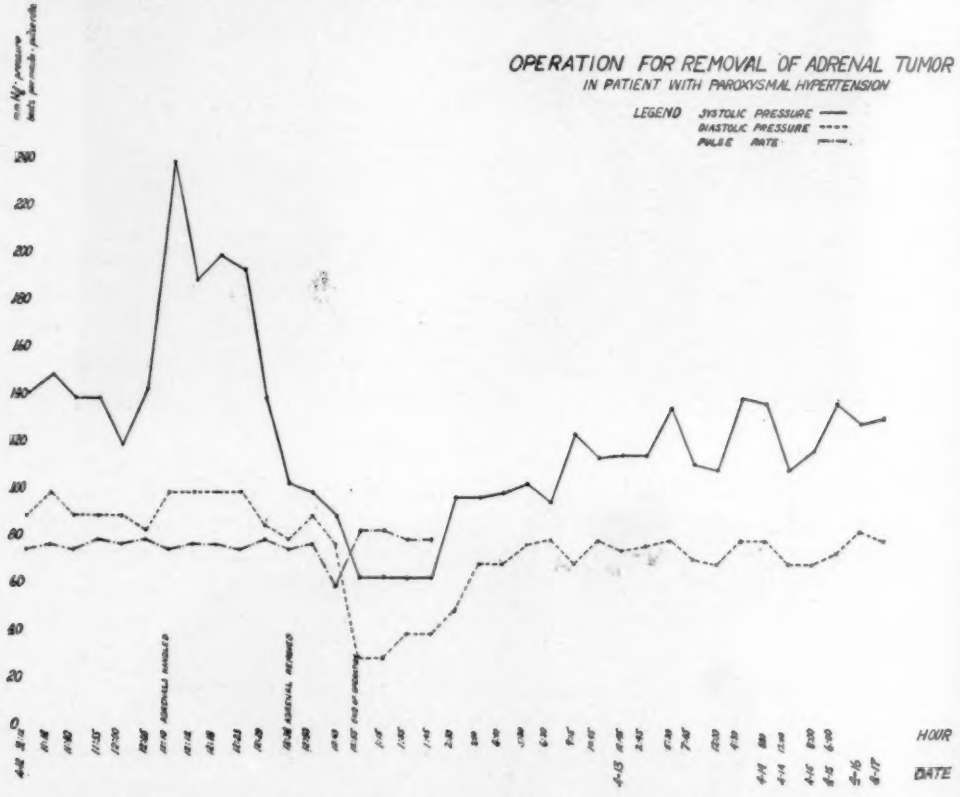

Fig. 6.—Blood pressure changes induced by handling adrenal gland at operation, showing fall of pressure following removal of gland and gradual return to normal over a period of two days.

of the gland was only 1 mm. thick. There was next a thin layer of rather acellular fibrous tissue. The tissue below this was composed of round or oval cells, some of which contained mitotic figures. Their cytoplasm was vacuolated; the cells remained in solid sheets. The pathologic diagnosis was pheochromocytoma of the right adrenal gland.

Extracts of the tissue were made by the trichloracetic method. The yield of adrenalin was equal to that of a normal gland. The specimen was frozen after removal in an effort to preserve the adrenalin from oxidation. This process may have delayed, but not completely stopped, the reaction of oxidation, and thus a portion of the yield may have been lost. Prior to the operation, two attacks were in-

duced with the intention of emptying the tumor of adrenalin and thus preventing a seizure during operation. However, a third attack did occur while the gland was being mobilized.

COMMENT

This patient's substernal compression and fear of impending dissolution at first suggested angina pectoris. He was conscious of fast heart rate and breathlessness, and was told that his face had marked pallor, followed by flushing. Sometimes there were nausea and vomiting. Later, extreme fatigability, tremor, and indisposition were noted. There were the characteristic paroxysms of hypertension, which have completely disappeared, with the other symptoms, since removal of the pheochromocytoma.

The differential diagnosis is usually limited to the group of hypertensive states, although pheochromocytomata may be present without a resulting hypertension. Essential hypertension is simulated, but the stimulation of the sympathetic nervous system is much more striking in those patients who have pheochromocytomata. The peripheral vessel change is dramatic in this group. The reactions are out of proportion to the physical findings between attacks. Similar symptoms and findings may be noticed in hyperplasia of the thyroid, as in toxic goiter, in which instance, however, the stimulation of the autonomic system is not as marked. The hypertension of toxic goiter is merely a rise in systolic pressure and is more usually sustained after it is once acquired. Again, the paroxysmal seizures are more clearly defined in medullary tumor. Cushing's syndrome simulates very closely adrenal cortical tumor and should be borne in mind in each instance in which disease of the adrenal gland is suspected. The important diagnostic points in pheochromocytoma are paroxysmal hypertension, increasing intolerance to glucose, and roentgenologic evidence of enlargement of an adrenal gland.

The reason for the paroxysmal type of hypertension is a matter of conjecture. Some writers feel that a psychic disturbance will cause an excretion of adrenalin because of the intimate manner in which these tumors are connected with the autonomic nervous system. Others feel that, because of the position of the gland, change in posture produces pressure and thereby stimulates excretion of adrenalin.

Briefly, the symptoms and signs of this condition are: a feeling that the heart is beating fast, breathlessness, pallor of the face followed by flushing, and sometimes nausea and vomiting. Later, extreme fatigability, tremor, and indisposition will be noted. There are usually a paroxysm of hypertension and an increase in pulse pressure, but a relatively slight increase in heart rate. The skin will be blanched and later flushed. There may or may not be glycosuria. There is a decrease in sugar tolerance. Signs of congestive heart failure may be present.

Excellent reviews of the earlier cases have been given by Rabin,[6] Eisenberg and Wallerstein,[7] and Belt and Powell.[8] The first mention of such a tumor was made by Frankel, in 1886. Manasse, in 1893, described the histopathology in detail, and later (1896) discovered the affinity of the tumor for the salts of chromic acid. Robert, in 1899, was the first to mention that hypertension existed in a patient with one of these tumors, although apparently he did not suspect the direct connection. In the thirty-seven cases reported prior to 1922 there was no definite suggestion of symptoms connected with these tumors. It is true that several operations were terminated suddenly with shock and death, and at intervals patients were known to have suffered hypertension. The first clinical description of paroxysmal hypertension was given in 1922 by Labbe, Tinel, and Doumer.[9] Their patient, a woman 28 years of age, suffered malaise, pallor, and the flushing of vasomotor instability, and died as the result of pulmonary edema. Paraganglioma was found at necropsy.

The first report of operative removal of such a tumor, with relief of symptoms, was made by C. H. Mayo (1927).[10] Further successful operations were reported by von der Muhll (1928),[11] Shipley (1929),[12] and Porter and Porter (1930).[13]

In 1934, Belt and Powell[8] attempted to remove a pheochromocytoma in a patient with paroxysmal hypertension. The shock was too great and the operation was terminated prematurely, the patient dying shortly afterward. Their failure to make a correct clinical diagnosis in this patient who, they felt afterward, presented such an extraordinarily dramatic group of signs and symptoms, was the stimulus for their excellent study of the clinical syndrome associated with the pheochromocytomata of the suprarenal medulla.

In this same year (1934), successful operations were reported by Coller, Field and Durant,[14] and by Suermondt.[15] Labbe and Nepveux[16] described a case of paroxysmal hypertension in which the patient was cured by removal of a paraganglionoma which had arisen from chromaffin tissue outside of the adrenal gland. The follow-up period was not given, but a statement was made that the blood pressure had become stabilized at 140/100. Kalk[17] described a typical case with paroxysmal hypertension and successful operation. Bauer and Leriche[18] recorded paraganglioma of the splanchnic nerve. Donzelot's case[19] was typical, and complete recovery on removal of the tumor occurred. Ernould and Picard[20] showed that paroxysmal hypertension was present in a patient with a malignant tumor, the presence of which was betrayed by metastases to the skull and various parts of the body. Laubry and Bernal[21] followed a patient with paroxysmal hypertension which later became fixed; the patient finally died in uremia.

In 1935, McKenna and Hines[22] removed a malignant paraganglioma from a patient with a variable hypertension and reported that the patient had been symptom-free for four months thereafter. Kelly,

et al.[23] (1936), Landau, et al.[24] (1936), and Beer, King, and Prinzmetal[25] (1937), have reported successful operations for removal of tumors in patients with typical symptoms. Information in the latter article is of value in that adrenalin is proved to be the pressor substance by clinical and laboratory tests upon the blood of the patient.

Kremer[26] (1936) reported a typical case with paroxysmal hypertension, in which death was due to pulmonary edema. Fein and Carman[27] (1937) reported medullary carcinoma, with large quantities of adrenalin per unit volume. The blood pressure was consistently low. Wells and Boman[28] (1937) reported a case in which the typical clinical syndrome was not recognized by five physicians, the patient subsequently dying of operative shock following removal of an acutely inflamed appendix.

In an analysis of the cases reported, there is little variation as to sex; of the 68 in which the sex was recorded 35 were women and 33 were men. As to age, the predominance lies in the middle decades, about equally in the third, fourth, and fifth, although a tumor has been found in a child 2½ years of age and in a man of 82 years. There are, however, eight cases in which the age was not mentioned. Of the symptoms, the most frequent are those of vasomotor instability, namely, palpitation, headache, nausea, and vomiting. Dyspnea, weakness, dizziness, fatigability, pain over the precordium, diaphoresis, sialorrhea, insomnia, convulsions, and sense of hair pulling are mentioned likewise.

In thirty-six instances the blood pressure was not recorded. Of the remainder, the paroxysmal type was noted in twenty-two, the constant type in nineteen, and in three the pressure was said to be normal. In retrospect, however, studies of these histories with regard to the incidence of hypertension are not reliable. In those reports in which no pressure is recorded, it is only assumption that the pressures were normal.

The tumors vary in size and weight up to 10.5 cm. and 1,000 gm., respectively. They are found about twice as often on the right as on the left side. In six instances they were found bilaterally. In seven instances they were said to be malignant because of evidence of metastasis.

In association with pheochromocytoma, von Recklinghausen's disease was present in five, tuberculosis in five, Addison's disease and melanoderma in one each, and diabetes in five. Of course, the diagnosis of diabetes may be rightfully doubted, as the evidence is based on glycosuria alone. Some of these patients may have had hyperglycemia because of hyperadrenalinemia and a low kidney threshold, and, therefore, definite proof of pancreatic disease is lacking.

Of the forty-one cases in which hypertension was found, there were but three with evidence of kidney change and but two with atherosclerosis.

TABLE I

RECORDED INSTANCES OF HYPERTENSION ATTRIBUTED TO HYPERPLASIA OR TUMOR OF THE ADRENAL CORTEX

YEAR	CASE	SEX	AGE	BLOOD PRESSURE	PATHOLOGIC FINDINGS		REMARKS
					OPERATION	AUTOPSY	
1921	Achard, Thiers[29]	F	71	220/100	None. Died 16th day after admission to hospital.	Adrenals large, right, 9 gm.; left, 7 gm. Hyperplasia cortex. Pituitary and thyroid normal.	Heavy moustache and beard only stigmas of virilism; menstruation 12 to 60 years. Glycosuria discovered at age of 69 by accident; no diabetic symptoms. "Diabetes of bearded women." Died 16th day.
1924	Walters and Keyser[30]	F	37	124/90 to 180/110	Tumor attached to left kidney removed.	Carcinoma suprarenal. Hypoplasia right suprarenal gland.	Genitosuprarenal syndrome, striking changes in sex characteristics. Enlargement thyroid, nervousness, tremor, tachycardia, heat intolerance. Pituitary, pineal bodies, and ovaries normal at autopsy. Died 4th day following operation.
1924	Oppenheimer and Fishberg[31]	M	24	200/150	None. Diagnosis of essential hypertension made. Tumor found only at autopsy.	Right, large tumor cortex and medulla. Left, 10 small cortical adenomas (10 gm. total weight)	Had acromegalic appearance. Renal function intact. Died of bronchopneumonia a few weeks after first seen.
	Ibid.	F	12	190/130	None.	----------	Genitosuprarenal syndrome. Blood sugar 260 mg. %. Abscesses on back and neck, ulcers on legs. Patient could not be followed, but it was reported that she died 3 weeks after leaving hospital.
1927	Murray and Simpson[32]	F	36	200/120	Suprarenal tumor removed.	----------	Amenorrhea 9 months before operation; insatiable appetite, with gain in weight. Following operation, menstrual function restored; appetite and weight returned to normal. Systolic blood pressure as a rule only about 120, but easily raised to 190 or 200 on slight excitement.

TABLE I—CONT'D

1929	Faber[33]	F	48	240/110	None.	Cortical adenomas; chronic nephritis, etc., marked congestion anterior lobe pituitary.	Author remarks that findings in this case, with the exception of suprarenal changes, are those of long-standing hypertension. Believes it impossible to say whether kidney and blood vessel disease or disease of suprarenals was causative factor.
1931	Hunter, McMillan, Boyd, and Cameron[34]	F	30	185/122	Tumor detached from vaginal wall by finger.	----------	Virilism; suppression of menstruation; diabetes mellitus. Mass felt in right upper abdomen, evidently connected with right kidney; no attempt made to remove this tumor. Roentgenogram showed metastatic lesions of chest and decalcification of vertebrae. No follow-up nor report of death on this patient.
1931	Meyer and Frumess[35]	F	13	158/85	None.	Primary carcinoma left suprarenal gland, with metastases. Large cortical adenoma, right.	Precocious development; hirsuties; suppression of menstruation, etc. No evidence of nephritis. Died 7 days after admission to hospital.
1932	Plazy and Germain[36]	M	40	200/80	None.	Cortical suprarenal tumor; aneurysm aorta; very numerous atheromatous patches on walls of aorta.	Authors believed that hypertension was due to the suprarenal tumor and that the tumor also explained the accompanying atheroma.
1933	Cecil[37]	F	31	170	720 gm. tumor removed.	Adenocarcinoma of left suprarenal.	Genitosuprarenal syndrome. Patient died 12 hours after operation of pulmonary hemorrhage.
1933	Shallow[38]	F	27	140 to 220	Suprarenal tumor removed. Histologic examination: adenoma, adrenal cortex.		Manifestations closely resembled Achard-Thiers syndrome. No improvement following operation. Died 5 months later of metastases.

TABLE I—CONT'D

YEAR	CASE	SEX	AGE	BLOOD PRESSURE	PATHOLOGIC FINDINGS		REMARKS
					OPERATION	AUTOPSY	
1933	Van der Bogert[39]	F	2	160/110 (Eyegrounds showed evid. hypertens.	Right adrenal shelled out subcortically.	None, except examination of tumor mass. Diagnosis: adrenal carcinoma.	Adrenal precocity. Sella extremely small roentgenologically. No autopsy, so lesions of pituitary and pineal could not be ruled out. Died within 36 hours after operation.
1933	Player and Lisser[40]	M	5	114/70 134/80	Left adrenal cortical tumor, possibly malignant.	----------	Sexual precocity. Nineteen months after removal of tumor blood pressure had dropped to 92/40. Some modifications of endocrine abnormalities.
1933	Quinby[41]	M	12	152/90 to 170	Large retroperitoneal tumor; not removed.	Micro. exam. report, evidently from biopsy: adrenal carcinoma.	Died following operation. Author believes that an adrenal cortical tumor of adenomatous character had been present many years, finally becoming malignant. Patient showed precocious puberty.
1934	Craig and Cran[42]	F	28	180/118	None.	Basophilic adenoma anterior lobe pituitary. Suprarenals deeply congested. Hyperplasia cortex.	Clinically diagnosed as basophilic adenoma. Author believes adrenal and thyroid changes were secondary. Roentgenotherapy; died of pneumococcic pneumonia.
1934	Leyton[43]	M	32	170	None	Tumor thymus gland, oat cell. Hyperplasia adrenal especially cortex. No excess basophilic cells, pituitary, in serial sections.	Multiglandular disease. Face and abdomen obese and legs slender. Broad purple lineae atrophicae from pubis over abdomen, etc. Sella appeared normal.

TABLE I—CONT'D

1934	Walters, Wilder, and Kepler[44]	F	25	180/120	Adenocarcinoma.	----------	Blood pressure returned to normal after operation. Right suprarenal gland found replaced by adenocarcinoma containing tissue of suprarenal origin. Patient had gained weight; menses had ceased, etc.
	Ibid. No. 2	F	9	132/97	Cortical adenoma, left adrenal.	----------	Genitosuprarenal syndrome began at age of 4 years. Within 3 weeks following operation weight had fallen; excessive hair disappearing. Blood pressure 98/62, 2 months later.
	Ibid. No. 3	F	39	170/102	Tumor, left suprarenal. Adenocarcinoma.	----------	Blood pressure 130/76, 2 months following operation. Face had regained normal contours, etc. Had had increase in weight, falling hair, scalp, increased hair on body.
	Ibid. No. 6	F	45	176/80	None.	Both suprarenals hyperplastic, combined weight 49 gm. Pituitary normal. Thymic tumor present.	Face heavy, dusky red; at times tetany present; died 2 months after admission to hospital. Thyroid previously operated upon. Multiple adenomas at autopsy in colloid thyroid.
	Ibid. No. 7	F	32	168/118	Exploratory; adrenal glands definitely enlarged.	Combined weight suprarenals estimated twice normal. Pituitary normal.	Hirsuties, irregular menstruation, etc. Died after 10th day, pneumonia. Portion adrenals removed at exploratory operation appeared normal histologically.
	Ibid. No. 8	F	30	150/100	Enlargement of both adrenals, hyperplasia tissue.	----------	Cortical adrenal syndrome disappeared after operation for most part. Blood pressure 124/62.

TABLE I—CONT'D

YEAR	CASE	SEX	AGE	BLOOD PRESSURE	PATHOLOGIC FINDINGS		REMARKS
					OPERATION	AUTOPSY	
1935	Lescher[45]	F	35	205/155	Suprarenal tumor, left removed.	Cortical cell carcinoma	Symptoms and signs of Cushing's disease. Died 12 hours after operation. Examination pituitary at autopsy did show general increase in basophiles and acidophile cells. Broster and Vines stain positive.
1935	Goldzieher and Koster[46]	F	27	180/100 after operation (not given before)	Left adrenal removed; both larger than normal.	----------	Had gained weight to 335 lbs.; missed periods; hirsutism present. After operation weight reduced to 190; periods regular. Blood pressure 180/100.
1935	Volini and O'Brien[47]	M	23	205/104	Tumor removed.	Malignant adenoma of suprarenal cortex.	Died in shock. Suprareno-cortical syndrome had been exhibited.
1935	Hare, Ross, and Crooke[48]	F	--	205/140	Suprarenal tumor removed.	Malignant suprarenal tumor. No pituitary tumor.	Had all signs of Cushing's syndrome, but in serial sections of pituitary no basophilic tumor found. Patient died in shock.
1935	Calder and Porro[49]	F	34	160/100 to 190/130	None. Roentgenotherapy; no benefit.	Primary adrenal neoplasm cortex.	Thought clinically to be instance of pituitary basophilism, but at autopsy pituitary was normal. Died 15 months after observation in hospital.
1935	Lyall[50]	F	30	210/120	Decompression operation. (Died following day.)	Carcinoma suprarenal.	Diagnosed as case of cerebral tumor. Eyesight failing, tingling, etc. Also obese, hirsutism, etc. Died day following operation.
1936	White[51]	F	37	155/100 variable	Exploratory only.	Adrenal cortical carcinoma (biopsy).	Patient showed all features commonly associated with adrenal cortical tumor. Subsequent course rapidly downward.

SUMMARY

This paper summarizes, first, the clinical instances that we have been able to find in the literature of hypertension ascribed to hyperplasia or tumor of the cortex of the adrenal gland. To this group we have added one case of our own which is unlike other reported instances in that marked hyperplasia of the adrenal cortex and a cortical adenoma were apparently responsible for the development of hypertension in a patient with evident cardiac decompensation.

The second presentation records the story of a patient in whom a diagnosis of pheochromocytoma of the adrenal medulla was made, with complete disappearance of the symptoms following surgical removal of the tumor.

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STUDIES ON CORONARY CIRCULATION

VI. The Effect of Some Members of the Digitalis Group on the Coronary Circulation*

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DRUGS which have generally beneficial effects on cardiac function may, at the same time, cause an undesirable alteration in the coronary circulation. It is, therefore, important to determine whether such a change occurs, and whether this change is of sufficient magnitude to be detrimental to efficient cardiac function. If it is definitely established that a drug has a constrictor action, it might be wise to consider the desirability of supplementing its action by the use of a known coronary dilator.

Since the members of the digitalis group are widely used in cardiac therapy, an exact knowledge of the pharmacologic action of these drugs is necessary in order to obtain the most satisfactory results from their use. We are particularly interested in the effect of this group of drugs on the coronary circulation. In the extensive literature and the large amount of experimental data on this problem contradictory opinions still exist regarding the effect of the digitalis bodies on the coronary circulation.

In the past it has been suggested that any undesirable coronary constrictor action of digitalis which might occur is, to a certain extent, counterbalanced by an improvement in myocardial contraction and the resultant increase in blood pressure. However, it is possible that the increased myocardial contraction actually interferes with the coronary flow, as Anrep[1] has demonstrated, and thus produces a further functional reduction in flow in a heart already embarrassed by disease or malnutrition.

The action of strophanthin and digitoxin upon the coronary circulation was studied by Loeb,[2] who perfused the excised heart of the cat with solutions of the drugs. According to his findings, strophanthin caused no appreciable change and digitoxin caused some reduction in the coronary flow. Later, Bond[3] reported that strophanthin and digitalis had no effect on the velocity of coronary flow in the intact cat. Voegtlin and Macht[4] investigated the direct action of an extensive series of drugs of the digitalis group on chains of coronary arterial

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rings. One of two digitalin preparations, digitalein, one of two strophanthin preparations, and a tincture of digitalis caused various degrees of contraction. They described digitoxin as the "most powerful coronary vasoconstricting constituent of digitalis leaf." Digitonin, digalen, and a digitalis infusion caused relaxation.

Gunn[5] reported that perfusion of the rabbit's heart at 28 to 41° C. with dilute solutions of crystalline strophanthin in nonglucose Ringer's solution caused "little or no constriction of coronary vessels."

With the description of the tampon cannula by Morawitz (1912), study of the minute volume of coronary blood flow was facilitated. Since its introduction several investigators have used this instrument in attempts to determine the effect of the digitalis bodies on the coronary circulation.

Sakai and Saneyoshi,[6] investigating the action of strophanthin on the intact cat preparation, concluded that this drug in small doses (0.01 mg.) has no direct action on the coronary vessels. According to these investigators, the increased volume of blood collected from the coronary sinus is entirely dependent on the changes in blood pressure. Larger, apparently toxic, doses of 0.2 to 0.5 mg., caused, almost always, an early fall in coronary outflow associated with a rise in blood pressure (constriction); later, in some instances, this trend was reversed and the flow increased.

Gilbert and Fenn[7] made an extensive study of the effect of digitalis on the coronary flow of intact dogs and concluded that digitalis bodies may have a vasoconstrictor action on the coronary arteries. They state that certain whole leaf preparations purchased on the open market produced constriction in the majority of their animals; one whole leaf preparation, however, had no constrictor effect. Ouabain had less constrictor action than did the whole leaf preparations. The two digitoxin preparations which they investigated caused variable responses, although there was some evidence of a coronary constrictor action. Bodo[8] investigated the changes in heart tone and coronary outflow in heart-lung preparations of dogs after administration of a number of drugs. He concluded that digitalis and strophanthin produce a moderate increase in the coronary flow.

Anrep[1] has stated that the Starling heart-lung preparation combined with the Morawitz method of collecting the coronary blood, using the same technique of measuring the blood flow in the intact animal, is the proper and the valuable technique. However, the findings with either preparation must be verified by similar determinations in the other. We have, therefore, made an extensive study of various digitalis preparations on denervated heart-lung preparations from both normal and previously digitalized dogs, supplemented by a large number of experiments on intact dogs. While we fully appreciate the fact that experimental work on normal hearts may give results which are not necessarily

TABLE I

CHANGES IN CORONARY SINUS OUTFLOW AFTER ADMINISTRATION OF SINGLE DOSES OF DIGITALIS BODIES IN DENERVATED HEART-LUNG PREPARATIONS*

DRUG	EARLY				LATE			
	TOTAL ANIMALS	DECREASE	NO CHANGE	INCREASE	DECREASE	NO CHANGE	INCREASE	NO DATA
Nondigitalized animals								
Digalen	5	1	2	2	0	4	0	1
Digifoline	3	3	0	0	0	0	3	0
Digiglusin	3	3	0	0	0	0	2	1
Scillaren	7	7	0	0	0	1	6	0
Strophanthin	7	7	0	0	0	0	6	1
Digitalis Tr.	15	13	2	0	3	3	7	2
Digitalis Tr.†	5	5	0	0	1	1	3	0
Total	45	39 (87%)	4 (8%)	2 (4%)	4 (8%)	9 (20%)	27 (60%)	5 (11%)
Digitalized animals Digiglusin	8	8	0	0	2	0	6	0
Grand Total	53	47 (89%)	4 (8%)	2 (3%)	6 (11%)	9 (17%)	33 (62%)	5 (9%)

*_Early_ refers to first ten-minute period after injection; _late_, to any subsequent change within forty minutes after injection. The column headed _No Data_ includes experiments which are not considered in the Late period because of some change in the experimental condition, e.g., altered respiration, or venous return, etc.

†After atropine.

duplicated in diseased hearts, such experiments do help in determining the action of the drug under investigation, and thus aid in analyzing its true therapeutic value.

METHOD

The members of the digitalis group used in this investigation were bought on the open market, namely, fresh tinctures and digiglusin (Eli Lilly and Company), fresh tinctures (Sharp & Dohme), and ampoules of digalen, digifoline, strophanthin, and scillaren. As in previous studies,[9, 10] we employed the Starling denervated heart-lung preparation as the most satisfactory method of determining the direct effect of these drugs on the coronary vessels. With this preparation all central action is eliminated, blood pressure can be maintained at a relatively constant level, and major variations resulting from changes in carbon dioxide and oxygen concentration are eliminated because of the constancy of artificial respiration. The temperature is maintained by passing the returned blood through a constant temperature bath. In both the heart-lung and intact animal preparations, the Morawitz cannula is introduced into the coronary sinus through the right auricle.

RESULTS

A. The Denervated Heart-Lung Preparation.—We determined the effect of a single injection of various members of the digitalis group on the coronary flow of fifty-three dogs (Table I). In forty-seven of these preparations there was a decrease in flow within the first ten-minute period following the injection. This decrease is the most consistent response observed in the heart-lung preparation and was obtained following the administration of all the drugs except digalen.

A small dose of digalen in one preparation caused a slight decrease, in two others, no significant change, and in the remaining two animals, an increase in the coronary flow. These changes occurred during the first ten-minute period following the injection (Table I). Repeated injections of this drug produced a similar response.

Fig. 1 graphically illustrates the average coronary flow and blood pressure in a number of heart-lung preparations for the ten-minute period immediately preceding and for successive ten-minute periods following the injection of the drug tested. The effect of a single injection of strophanthin (*B*), scillaren (*C*), and digitalis tincture, digiglusin and digifoline (*D*) was a decrease in coronary flow shortly after the injection, occurring simultaneously with a rise in blood pressure. This was then followed by an increase in coronary flow, often (*B* and *D*) exceeding the original volume, and by a fall in blood pressure to approximately the initial level. Atropine administered to the animal before the injection of digitalis tincture had no appreciable effect upon the response, as is evident in *E*.

Since there is a possibility that a single dose of 1 or 2 cat units of digitalis tincture might possibly cause constriction in the dog's heart as a toxic manifestation, a number of experiments were carried out in which this amount was divided and injected in equal portions at five-

or ten-minute intervals. Fig. 2*B* illustrates the results of four such experiments in which injections were made at five-minute intervals. Similar results were obtained with this method of administration as with the single dose method. Comparing the curves in Fig. 1 and Fig.

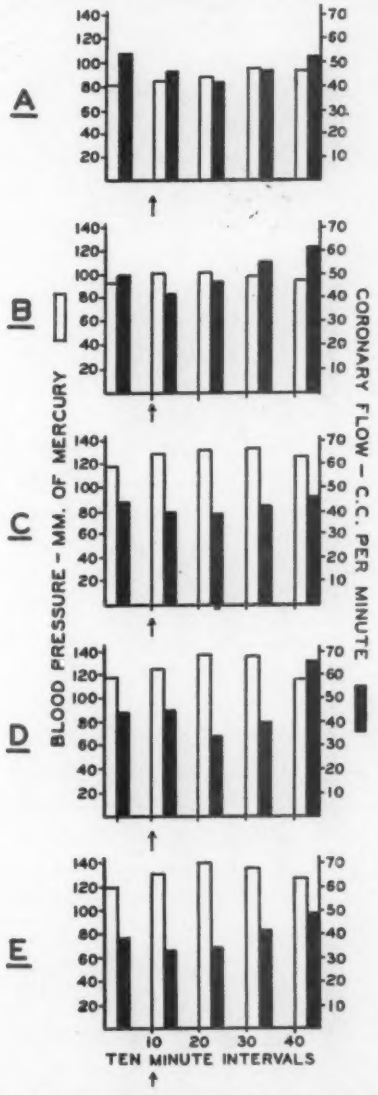

Fig. 1.—The coronary sinus outflow (black) and blood pressure (white) in heart-lung preparations. *A*, Average of results from six digitalized dogs. First column represents preinjection blood pressure and coronary sinus outflow. At arrow, one cat unit of digiglusin was injected into the venous return. Each block represents the average for five-minute periods. *B*, Same as *A* except that the one animal used was not previously digitalized. The blocks represent averages for ten-minute periods. At arrow, ¼ c.c. strophanthin was injected. *C*, Same as *B* except that five nondigitalized animals were used. At arrow, ¾ c.c. scillaren was injected. *D*, Same as *C* except that eight nondigitalized animals were used and at arrow, ½ cat unit (two dogs) or two cat units (six dogs) of tincture of digitalis was injected. *E*, Same as *D* except that the five preparations used were atropinized before the injection of tincture of digitalis (one cat unit).

2*B*, one can see that the constriction which results from the repeated injections of small doses comes on more gradually than after a single dose. The increase in coronary flow begins approximately at the same time in both cases.

Since a late increase in coronary flow was so frequent in intact and heart-lung preparations after both single and repeated injections, it seemed desirable to determine what effect, if any, preliminary digitalization of the animal would have on the coronary response to digitalis.

Twenty-six animals were digitalized according to the dosage scheme of Eggleston, as described by Sollmann.[11] The drug was administered intravenously after dilution with saline solution. We have compared the electrocardiographic changes occurring in our intact unanesthetized dogs after digitalis administration with the electrocardiographic changes in fifteen normal human subjects reported by Larsen and his co-workers.[12] These investigators found a lowering of the T-wave, a depression of the S-T interval, and a lengthened Q-T interval in most of their subjects. The electrocardiographic changes which we obtained in dogs, following the administration of digitalis in comparable therapeutic doses, were essentially the same as those described by Larsen and therefore were considered to be indicative of complete digitalization. Additional investigations are now in progress to determine the electrocardiographic changes following digitalization.

Of these twenty-six digitalized animals, eight were used as denervated heart-lung preparations. The data recorded in Table I and Fig. 1*A* show that the injection of a single cat unit of digiglusin caused a consistent fall in the coronary flow shortly after the injection and a rise in coronary flow later in the experiment. The blood pressure did not fall during the later periods of the experiment (compare with 1*D*) but remained fairly constant at some level usually above the original pressure. During the course of these experiments, it was observed that the digitalized heart is much more sensitive to the mechanical trauma incident to the surgical procedures, necessitating extreme care in preparation. The period required for satisfactory stabilization of coronary flow and blood pressure before injection was frequently much longer than that required for the similar stabilization of a nondigitalized dog.

B. The Intact Animal.—The results obtained when intact animals were used to test the action of the same series of drugs were not so consistent as those in the heart-lung preparations. Of forty-seven such determinations, an early decrease in coronary outflow was recorded in twenty (Table II); in fifteen, there was no significant change; in twelve, there was a definite increase. The number of experiments in which digalen, digifoline and digitalis tincture were administered in single doses to intact animals, as indicated in Table II, seems too small to merit any specific comment on their action. Additional experiments with these

drugs, which, for various reasons, are not included in Table II, yielded results which are similar to our other observations. The response to digalen was the least consistent of all the drugs studied; the results obtained with digifoline and digitalis tincture in the intact animal were essentially the same (Table II). Judging from our results on the intact animal, strophanthin must be considered as causing a definite early coronary constriction in most cases, which is followed by a later increase in outflow.

When the dose of digitalis tincture was divided into equal portions and administered to intact dogs at five-minute intervals, the effect was essentially the same as if administered in a single dose (Figs. 2*A* and

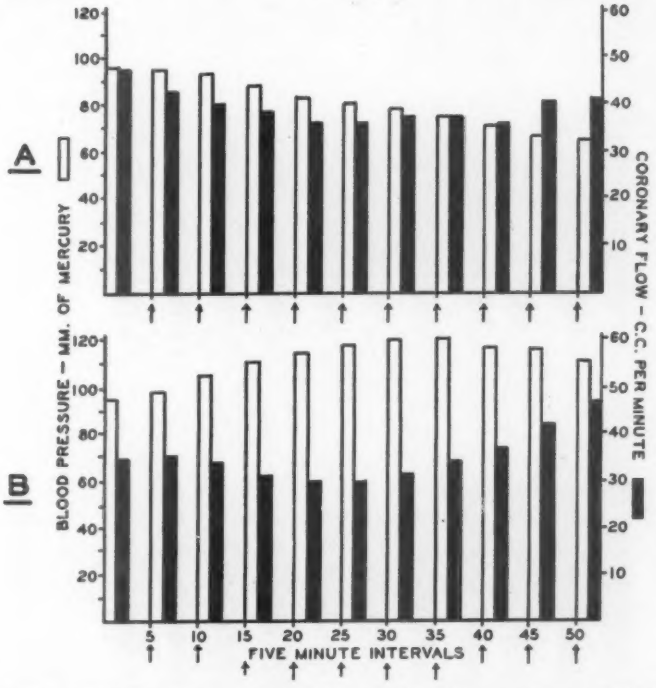

Fig. 2.—The coronary sinus outflow (black) and blood pressure (white) after repeated small injections of digitalis tincture. *A*, Average of the results from four intact dogs. The first column represents the preinjection blood pressure and coronary sinus outflow. Each arrow indicates the injection of 0.1 cat unit of digitalis tincture. *B*, Average of the results from seven heart-lung preparations in which five animals received 0.1 cat unit and two animals received 0.2 cat unit of digitalis tincture at five-minute intervals.

3*A*). In some cases the appearance of the early reduction and later increase in coronary flow were delayed, although this is not evident from Fig. 2*A*.

The modification of the response to digiglusin after preliminary digitalization was striking (Fig. 3*A* and *B*). In nondigitalized animals receiving the first dose of this drug at the time of the experiment, the flow was reduced in only four of twelve animals; there was no change in seven; and there was an increase in one (Table II). Later in the

TABLE II

CHANGES IN CORONARY SINUS OUTFLOW AFTER ADMINISTRATION OF SINGLE DOSES OF DIGITALIS BODIES IN THE INTACT ANIMAL*

DRUG	EARLY				LATE			
	TOTAL ANIMALS	DECREASE	NO CHANGE	INCREASE	DECREASE	NO CHANGE	INCREASE	NO DATA
Nondigitalized animals								
Digalen	1	1	0	0	0	0	1	0
Digifoline	1	0	0	1	0	0	0	1
Digiglusin	12	4	7	1	0	4	7	1
Scillaren	4	1	2	1	0	3	1	0
Strophanthin	9	6	3	0	0	2	6	1
Digitalis Tr.	3	1	0	2	0	0	2	1
Total	30	13 (43%)	12 (40%)	5 (16%)	0 (0%)	9 (30%)	17 (56%)	4 (13%)
Digitalized animals Digiglusin	17	7	3	7	0	2	13	2
Grand Total	47	20 (43%)	15 (32%)	12 (25%)	0 (0%)	11 (23%)	30 (64%)	6 (13%)

*See first footnote, Table I.

experiment, an increase in flow to some point above the original level was recorded in seven animals, while this level was reattained in four animals. In the seventeen animals that were digitalized preliminary to the experiment (Table II), there was a decrease in the coronary outflow in seven, an increase in seven, and no significant change in three. In the later portion of the experiment, thirteen of the seventeen exhibited an increase in flow, which, while not very marked, is very significant in view of the simultaneous decline in blood pressure.

DISCUSSION

The results which we are reporting, i.e., an early decrease followed by an increase in coronary flow after the administration of digitalis, might account for the contradictory conclusions reached by previous investi-

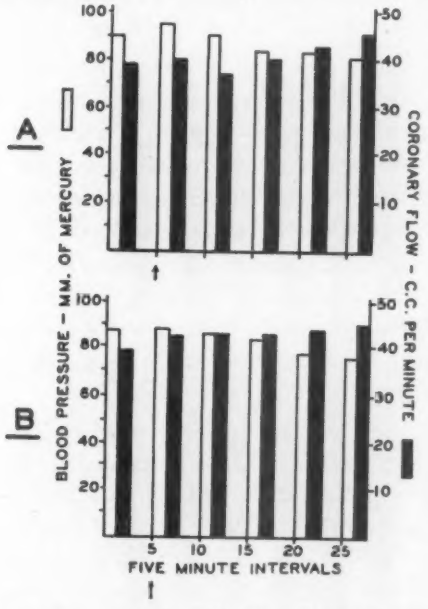

Fig. 3.—The coronary sinus outflow (black) and blood pressure (white) in nondigitalized and digitalized intact animals after a single injection of digiglusin or digifoline. *A*, Average of the results from eight intact nondigitalized dogs. The first column represents the preinjection blood pressure and coronary sinus outflow. The arrow indicates the single injection of 1 c.c. (six dogs), 0.66 c.c. (one dog), or 0.25 c.c. (one dog) of digiglusin or digifoline. *B*, Average of the results from twelve digitalized intact dogs after a single injection of 0.02 c.c. digiglusin per kilogram of body weight.

gators as to the effect of the digitalis bodies on the coronary circulation. If only the early effect of digitalis on the coronary flow is considered, the evidence will be in favor of a reduced flow caused possibly by constriction of the coronary vessels. If only the late effect, i.e., the increased flow which almost always follows this early reduction in both the heart-lung preparation and the intact animal is considered, the conclusion might be either that no significant change in flow had occurred or that the flow was increased. In most of our animals any

detrimental effects of the decrease which occurred during the ten-minute period immediately following the injection might be compensated for by the beneficial effects of the increase during the next period of twenty or more minutes.

In our series of experiments the changes in the coronary blood flow were as consistent in the atropinized heart-lung preparations as they were in the nonatropinized preparations. These results indicate that the alteration in coronary flow after digitalis administration is due to a direct action of the drug on the myocardium or the coronary vessels, rather than on the extrinsic nervous mechanism. These findings are not in agreement with those of Gilbert and Fenn,[7] who found that in either the vagotomized or the atropinized animal there was no decrease in coronary flow which could not be accounted for by the change in blood pressure.

It is possible that the decrease in coronary flow which follows a single injection of digitalis may cause an anoxemia which is responsible for the later dilation of the coronary vessels. While our results on digitalized animals are not strikingly different from those on nondigitalized animals, they do demonstrate that repeated injections of digitalis bodies do not lead to an unfavorable reduction in blood flow through the myocardium; on the contrary, there is a greater tendency to increased flow in the intact animal which has been digitalized. We observed that the hearts of digitalized animals tend to be hypersensitive to experimental manipulations, which often results in a marked irregularity in action or a slower rate of contraction.

Clinical investigations on the tendency of digitalis to increase the frequency of cardiac pains in patients suffering from angina have been reviewed by Fenn and Gilbert.[13] These investigators stated that in some of their patients angina pectoris attacks developed as a result of digitalis treatment. More recently, Gold, et al.,[14] have made an extensive investigation of the severity and frequency of cardiac pain in patients suffering from cardiac disease, none of whom had signs of congestive heart failure. All patients studied had pain on effort. After a course of treatment with digitalis, 15 per cent of their patients reported an increase in pain, while in 30 per cent the pain was diminished. Similar results were obtained during the use of a placebo. On the basis of their results they came to the conclusion that in cases of angina pectoris without congestion there is very little likelihood that the use of digitalis will, by direct action on the circulation, increase or diminish cardiac pain.

This conclusion is not inconsistent with the results we have obtained on dogs. The reduction in coronary flow which we and others have recorded is never of sufficient magnitude to cause much disturbance of cardiac function. The fairly constant increase of coronary blood flow

which follows the initial decrease would soon counteract any unfavorable condition that might have occurred. Since reduction in coronary flow is more marked and more constant in the heart-lung preparation than in the intact animal after digitalis, it seems reasonable to conclude that even if digitalis has a direct constrictor action upon the coronary vessels the other circulatory changes which follow the administration of this drug are such that the coronary flow is not reduced markedly despite the constriction.

The increased coronary blood flow which follows the period of reduced flow is probably the result of the improvement in the general circulation which is caused by digitalis.

SUMMARY

1. The effect of various digitalis preparations on the coronary sinus outflow of heart-lung preparations and intact dogs was studied.

2. In the heart-lung preparations the most consistent effect was a decrease in the coronary flow during a period of about ten minutes. This was, in most cases, followed by an increase in the coronary flow which persisted throughout the remainder of the experimental period.

3. Similar results were obtained in intact animals, but they were not so definite. In many of these animals no appreciable change in the coronary flow occurred; in others, there was a slight increase.

4. In heart-lung preparations from digitalized dogs, the injection of digitalis bodies led to a decrease in coronary flow for about ten minutes. This was followed by an increase which persisted throughout the remainder of the experimental period.

5. In intact digitalized dogs the injection of digitalis bodies produced an increase in the coronary flow which was preceded by very little, if any, decrease.

6. Our results would indicate that the constrictor effect of digitalis upon the coronary circulation is not of sufficient magnitude to contraindicate its use in cardiac disease, except in those cases in which there is a very marked deficiency in coronary circulation.

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THE MEASUREMENT OF VENOUS PRESSURE BY THE DIRECT METHOD*

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VENOUS pressure measurements are accepted as a definite aid in the diagnosis of "right-sided" heart failure. In our experience, however, they have been of relatively little assistance in the diagnosis of the borderline cases of congestive failure in which the use of a quantitative method is particularly important. One of the reasons for the difficulty of interpreting the measurement in any given patient is the degree of variation in the reports of venous pressures in normal people, as illustrated in Tables I and II.

There are in general two factors, aside from individual differences, which may explain this variation in the range of venous pressure in normal people: first, the variety of instrumental methods used; and second, the lack of uniformity in the definition of the "reference point," or the level at which the zero point of the manometer is set. Consideration of the method and the reference point is the purpose of this paper.

There are two related, but slightly different, definitions of peripheral venous pressure. One is concerned with the measurement of the actual pressure existing at a given moment in a given vein; this may be designated as "local" venous pressure. In this measurement the zero point of the manometer is set at the level of the vein itself. Such a measurement is concerned with local phenomena, such as the pressure and flow relationships between the capillaries and the veins to which they lead.

Venous pressure may also be considered in relation to the return of blood to the right auricle, and the measurement of such pressure expressed in terms which take into consideration the position of the right auricle. Pressure so expressed may be influenced by changes in the cardiac function; it may be designed as "general" venous pressure. In addition to the level of the auricle, a factor to be considered in relation to the general venous pressure is the intrathoracic pressure. The pressure influencing flow from extrathoracic veins to the auricle is actually the difference between the "general" (hydrostatic) venous pressure and the intrathoracic pressure. For example, if the pressure

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in the antecubital vein when referred to the level of the auricle is 50 mm. of water and the negative pressure in the thorax is 50 mm. of water then the total pressure influencing the flow of blood to the auricle is 100 mm. of water. This difference is usually referred to as the "effective" venous pressure. Ideally venous pressure should be expressed in terms of the effective pressure, actually the measurement of intrathoracic pressure is not practicable in most cases. The accuracy of the venous pressure determination is therefore handicapped at the start since it is possible that, under particular circumstances, changes in the intrathoracic pressure may affect the level of the pressures in the extrathoracic veins. This discussion will be concerned with what has been defined as "general" venous pressure without corrections for possible fluctuations in the intrathoracic pressure.

The pressure in a superficial vein may be evaluated by three general methods: (1) direct inspection and palpation of the vein; (2) determination of the pressure necessary to collapse the vein, the so-called "indirect" method; and (3) the measurement of the pressure exerted through a needle in the lumen of the vein, the "direct" method. This discussion will be limited to a consideration of the measurement of venous pressure by the direct method.

Though various types of apparatus have been used to measure venous pressure directly, the most widely used and on the whole the most satisfactory instrument is that described by Moritz and von Tabora.[1] This apparatus consists of a system of tubes filled with liquid, similar to that shown in Fig. 1. The manometer tube of this system can obviously be placed at any desired level regardless of the site of venipuncture. Appropriate use of this method permits repeated readings over considerable periods of time with a single venipuncture. In these studies the only modifications in the apparatus of Moritz and von Tabora were the addition of a side arm syringe and the substitution of normal saline for the citrate solution. Except for special observations, which will be designated, all measurements were made with the subject in the supine position.

In an attempt to evaluate the potential sources of error in the apparatus, consideration was given to the bore of the manometer, the size of the needles, and the length of the tubing. It is clear that in any method involving the measurement of pressure by the height of a fluid level in a small bore manometer, a source of error is introduced by the capillarity of the manometer tube. Manometers of 1 mm. bore, such as the usual spinal fluid manometer, have a capillarity (with water) of roughly 25 mm., whereas one of 2 mm. bore has a capillarity of roughly 12 mm. In larger tubing the capillarity is sufficiently small to be of no significance in venous pressure measurements. Throughout these studies a manometer of 2 mm. bore was used, which implies an error of 12 mm. in all reported readings.

Within the limits of gauge 14 to gauge 25 (inside diameter approximately 0.25 to 1.5 mm.), the size of the needle through which the pressure is measured imposes no error on the final pressure recorded, but influences the time required before a constant level is attained. Also, when the smaller needles are used, the system is less sensitive in reflecting minor changes in pressure, such as those observed in different phases of the cardiac or respiratory cycles.

No important errors were produced by minor variations in the length of the tubing. It is important, as in all methods using fluid in tubing, to be sure that air bubbles have been eliminated.

There is no agreement among observers as to the optimum position of the arm when the antecubital vein is used for the measurement of

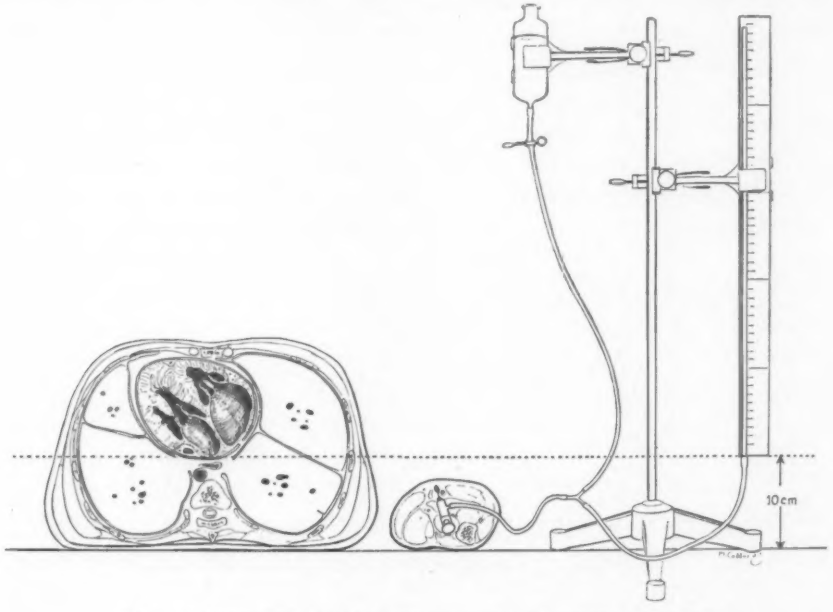

Fig. 1.—Apparatus for the measurement of venous pressure.

the venous pressure. Accordingly, this question was studied by observing the influence on the venous pressure readings of changes in the level of the elbow, in the degree of abduction of the shoulder, and in the supination or pronation of the forearm.

It is a common observation that when the arm is raised above the level of the heart the veins collapse. It has been demonstrated by Carrier and Rehberg[2] and by von Recklinghausen[3] that, when the hand is raised from below the heart level upward and the point of reference kept constant, the pressure in the veins in the dorsum of the hand decreases nearly proportionately to the decrease in the hydrostatic pressure. However, when the pressure in the antecubital vein is measured by the direct method as described, with the ante-

cubital vein at various positions above or below the assumed heart level, there is a different series of events. In 20 subjects in the supine position the pressure in the antecubital vein remained essentially unchanged when the elbow was raised or lowered, as long as it was not raised above a critical level near the center of the chest. The exact position of this level varied considerably in different individuals, but when the elbow was raised above it the pressure in the antecubital vein tended to *rise*. In general, the higher the site of venipuncture was raised above this level the greater was the increase in the venous pressure. Examples of these results are shown in Fig. 2. This eleva-

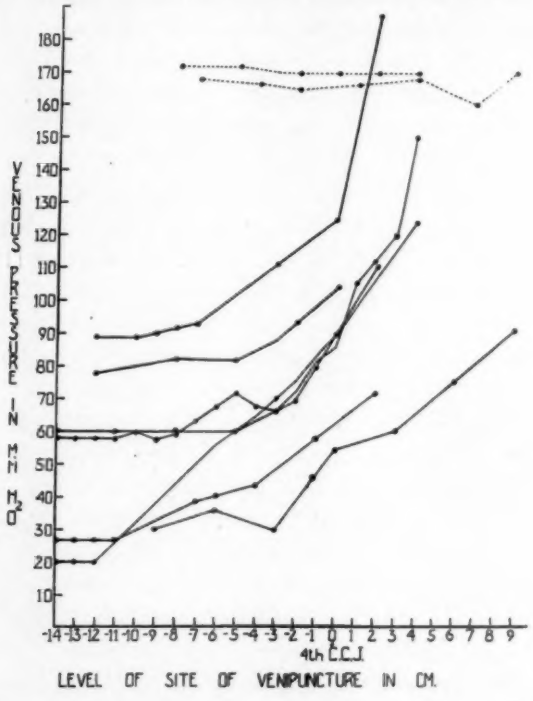

Fig. 2.—Change of venous pressure with elevation of site of venipuncture. Venous pressure measured with the zero point of the manometer 5 cm. posterior to the fourth costochondral junction. The dotted lines represent two patients with heart failure. In this chart the abbreviation "C.C.J." refers to the costochondral junction.

tion of the venous pressure with change in the level of the site of venipuncture was not due to a change in the height of the column of blood in the distal veins because passive flexion of the elbow with elevation of the hand and forearm above the site of venipuncture did not change the pressure in the antecubital vein.

When this same procedure was applied to subjects with elevated venous pressure, no comparable change occurred, as is also shown in Fig. 2. This may suggest that the apparent increase in venous pressure in normal subjects was the result of (or was influenced by) a

collapse of the vein at some point between the site of venipuncture and the auricle—a collapse which does not occur under these circumstances in patients with sufficiently elevated venous pressures.

To evaluate the effect, if any, of abduction of the shoulder on the venous pressure, readings were made at 10-, 45- and 90-degree abduction. In a fair majority of cases the venous pressure varied slightly with changes in the abduction of the shoulder. Ten-degree abduction frequently gave slightly higher readings than 45-degree abduction. At 90-degree abduction the venous pressure was usually the same as at 45 degrees, but occasionally elevations of considerable magnitude would occur. In general, the lowest readings were obtained with 45-degree abduction.

Pronation and supination of the forearm made no difference in the venous pressure in most of the cases studied. A position of relaxation and comfort was more important than the degree of rotation of the forearm.

Certain variations in the physiologic state of the individual, such as muscular exertion, muscle tension, emotional tension, changes in the type of respiration, pain, and variations in the environmental temperature were also considered as possible distorting influences on the venous pressure.

It is well known that exercise is accompanied by an elevation in venous pressure.[4, 5, 6, 7, 8] The degree of this elevation and the time required for the venous pressure to return to a constant level after exertion depend on the extent of the exercise and on the functional capacity of the circulation in the individual. In patients with heart failure exertion is said to produce a greater elevation in venous pressure and one that lasts over a considerably longer time than in normal subjects. Consequently, the time required for the attainment of "standard" conditions with regard to venous pressure will vary with the degree of exertion just before the test, the ability of the subject to relax, and the state of the circulation. In normal subjects working about the laboratory, from four to eight minutes were required after cessation of activity before a constant venous pressure reading was reached.

Tension of groups of muscles caused no appreciable change in the venous pressure unless it directly affected the venous flow from the needle to the thorax. Movements of the thoracic muscles or arm muscles proximal to the site of venipuncture often caused a rise in the venous pressure. Movement of the diaphragm exerted a marked influence on the venous pressure, and minor activity, such as talking, appeared to distort the venous pressure, presumably through changes in the intrathoracic pressure.

Similar to the effects of muscular tension and perhaps related to them were those of emotional tension. Often in highly nervous sub-

jects the venous pressure readings were variable until adequate relaxation was obtained. The breathing of such subjects was at times quite irregular, which may in part explain transient changes in the venous pressure.

Frequently during continuous observations on relaxed subjects a drop in venous pressure of 5 to 40 mm. occurred directly following an unusually deep or sighing respiration. Falsely low readings may be recorded as a result of such transient fluctuations unless the respirations are carefully watched and the venous pressure is followed for several minutes.

In normal subjects an increase in the rate of respirations, shallow or deep, is accompanied by a fall in the venous pressure.[9, 10] In our observations this fall began at the onset of abnormal breathing, and the venous pressure tended to be maintained at the new low level until normal respirations were resumed. Holding the breath was accompanied by a rise in the venous pressure. Marked variations in pressure occurred with resisted expiratory effort from the inspiratory position of the chest (Valsalva experiment) and resisted inspiratory effort from the expiratory position of the chest (Müller experiment).

The pain that is occasionally elicited by venipuncture caused no definite effect on the venous pressure unless the subject tensed the diaphragm or other muscles. Discomfort is best avoided by the use of novocain at the site of venipuncture.

When heat dissipation remained unimpaired, variation in the environmental temperature within fairly wide limits (45 to 100° F.) had no effect on the venous pressure. When the temperature was so low that shivering occurred, there was a moderate rise in the venous pressure. Artificial fever, according to the work of Gibson and Kopp,[11] causes a considerable elevation of venous pressure when it is associated with capillary dilatation.

In a few individuals sudden transient increases in the venous pressure occurred during the test without any apparent external cause and when the subjects were conscious of no subjective changes. Venous spasm has been suggested to explain such changes, but in none of our cases was this directly observed.

In general, repeated readings in the same individual over several months, using the precautions outlined above, have shown little variation in the level of venous pressure. In a few patients, however, especially those who have difficulty in relaxing, variations of the order of 20 to 30 mm. occurred.

One of the most important elements in the technique of venous pressure measurement is the selection of the reference point, or the level at which the zero point of the manometer is set. There is no unanimity of opinion among observers as to the exact position of this point. Some have defined the level they use with accuracy; others

have indicated only that the zero point of the manometer should be set at "the level of the right auricle." It may be said that there is general agreement in the literature that the reference point should be at the level of the auricle, but there is considerable variety of opinion as to the location of this point in a given subject. This has led to the use of reference points which may vary from one another by as much as 50 mm., with a corresponding variation imposed on the venous pressure reading.

Three definitions of the reference point for the supine position have been used more frequently than others. Von Recklinghausen[3] defined the level of what he termed the venous reservoir as the midpoint of the thorax. Moritz and von Tabora[1] defined the level of the right auricle as 5 cm. dorsal to the fourth costochondral junction. Eyster[12] used the junction of the middle and anterior thirds of the thoracic diameter as the level of the reference point. Tables I and II list the reference points used by various authors in their studies of venous pressures in normal persons.

The suitability of these reference points has been tested by three sets of studies. First, post-mortem material and anatomical specimens have been examined to establish the location of the auricle in the thoracic cage. Second, in 42 normal subjects the apparent position of the auricle was determined by fluoroscopy and the venous pressure was measured in relation to the reference point so selected. Third, on the assumption that variation in the position of the reference point is a factor in the width of the range of venous pressure observed in normal people, a study of the various reference points in relation to this range has been made.

The results of these studies may now be considered. The position of the right auricle in its relationship to the front and back of the chest was studied in cross sections of 14 cadavers. These bodies had been frozen in the supine position, and the section had passed through the chest at the level of the tricuspid valve. In each of these specimens the posterior border of the right auricle was between 80 and 105 mm. anterior to the skin of the back. This measurement was from 40 to 50 per cent of the thoracic diameter. The most posterior portion of the heart at this level was usually the right auricle. The auricle itself measured from 40 to 70 mm. in anteroposterior diameter, and the anterior border was usually within 40 to 50 mm. of the anterior border of the thorax. These findings, and certain observations made at autopsies, led to the attempt to use the posterior border of the cardiac shadow in the fluoroscope (with the subject in the supine position) as an approximation to the level of the right auricle.

Using the precautions described in the first portion of this paper, the venous pressure was measured in 42 normal subjects in the supine position. With the fluoroscope the level of the posterior border of

the heart was then estimated with the subjects in the same position on the same table.* In these subjects the posterior border of the heart shadow lay from 65 to 100 mm. anterior to the skin of the back (35 to 55 per cent of the thoracic diameter). This is not very differ-

TABLE I

VENOUS PRESSURES OF NORMAL PERSONS BY DIRECT METHODS

DATE	AUTHOR	POSITION OF PATIENT	REFERENCE POINT	RANGE
	A. Saline-Filled System, e.g., Moritz and von Tabora			*mm. saline*
1910	Moritz and von Tabora[1]	Supine	5 cm. posterior to the 4th costochondral junction	10-90
1910	von Tabora[14]	Supine		80-120
1912	Schott[4]	Supine		44-130
1912	Frank and Reh[15]	Supine		10-60
1920	Arnoldi[16]	Supine		77-103
1920	Moog and Ehrmann[17]	Supine		Below 100
1921	Fuchs[18]	Supine		15-125
1922	Kroetz[19]	Supine		0-70
1924	Boas and Dooneief[20]	Supine		10-100
1924	Runge[21]	Supine	4th costochondral junction	48-60
1927	Blumgart and Weiss[22]	Supine	5 cm. posterior to the 4th costochondral junction	25-50
1928	Harris[23]	Supine	Anterior axillary line	50-75 25-150
1930	Ernst and Stagelschmidt[24]	Supine	5 cm. posterior to the 4th costochondral junction	Below 120
1930	Gönczy, Kiss, and Enyedy	Supine		55-112
1931	Brandt[27]	Supine		50-100
1932	Criep[27]	Supine		Average 102
1933	Brams, Katz, and Schutz[28]	Supine	Junction of anterior and middle thirds of thoracic diameter	45-135
1933	Harrison[29]	Supine	5 cm. posterior to the 4th costochondral junction	50-65
		Sitting	Level of right auricle	50-100
1934	Budelmann[30]	Supine	5 cm. posterior to the 4th costochondral junction	34-72
1934	Griffith, Chamberlain, and Kitchell[31]	Supine	2½ in. dorsal to angle of Louis	60-120
1935	Overholt and Pilcher[32]	Supine	5 cm. posterior to the 4th costochondral junction	Below 120
1935	Wood, Capaccio, and Weaver[33]	Supine		65-105
1935	Wartman[34]	Supine		60-120
1936	Krinsky and Gottlieb[9]	Supine		Average 11.8
1937	Ferris and Wilkins[35]	Supine		40-100
	B. Air-Filled System With Aneroid Manometer			*mm. water*
1914	Claude, Porak, and Rouillard[36]	Supine	----------	80-240
1921	Villaret, Saint-Girons, and Jacquemin-Guillaume[37]	Supine	----------	Below 130 ♂ Below 120 ♀
1922	Leconte and Yacoel[38]	Supine	----------	140 ♂ 120 ♀
1923	Castellotti[39]	Supine	----------	40-70
1923	Corradi[40]	Supine	----------	88-132
1923	Gazzotti[41]	Supine	----------	140 ♂ 130 ♀
1924	Bedford and Wright[42]	Supine	10 cm. below sternum at subcostal angle	5-150

*The authors acknowledge with gratitude the expert assistance of Dr. M. C. Sosman and Dr. John Larkin in studying these subjects with the fluoroscope.

TABLE I—CONT'D

DATE	AUTHOR	POSITION OF PATIENT	REFERENCE POINT	RANGE
	C. Blood-Filled System, e.g., L-Tube Method			*mm. blood*
1918	Marris[43]	Supine	----------	40-60
1923	Young[44]	Supine	"8 cm. deep from sternum"	100-140
1930	Taylor, Thomas, and Schleiter[45]	Supine	Midaxillary line	40-100
1932	Evans[46]	Supine	Midaxillary line	75-150
1934	Fishberg, Hitzig, and King[47]	Supine	5 cm. below sternum at 4th rib	40-80
1935	Robertson and Fetter[48]	Upright	"Right auricle"	90-125
1935	Kinsman and Moore[49]	?	?	20-150
1936	Cohen[50]	Supine	Right auricle	60-120
1936	Hussey[51]	Supine	Midaxillary line	40-120
1936	Wood[52]	45° upright	4th intercostal space	20-105
1937	Candel and Rabinowitz[53]	?	?	40-80
1937	Hurst and Brand[54]	?	Vein placed 4-5 cm. below right auricle	50-90
1937	Berger[55]	?	5 cm. below sternum at 4th intercostal space	Average 77
1937	Gibson and Evans[56]	Supine	Midaxillary line	40-130

ent from the observations made on cadavers, but, when these individually determined zero points were used in the measurement of venous pressure, the range of variation was greater than when any of the arbitrary zero points mentioned above was used. This wide variation may be due to the difficulties inherent in this method of establishing the level of the auricle.

The three arbitrary reference points mentioned are similar in that each of them is influenced by the anteroposterior diameter of the thorax. In the group of 42 cases so far considered there was relatively little variation in the size of the chest. The validity of these points was put to a further test by determining the venous pressure in 48 more normal subjects with widely different thoracic diameters. The two groups were combined and the analysis of the venous pressure measurements in these 90 patients is shown in Figs. 3, 4, and 5.

In general, it may be said that, when subjects with widely varying thoracic diameters are studied, there is a wide variation in the range of venous pressure as determined with these standard reference points and that there is a relationship between the size of the chest and the level of the venous pressure. It may even be said that with the use of these reference points, the greater the thoracic diameter the lower the apparent venous pressure tends to be (Fig. 6).

Now there is no reason to believe that individuals with large thoracic diameters should in fact have lower venous pressures than those with smaller chests. Indeed, the work of Kountz and others[13] has suggested that the contrary may be the case. It is therefore sug-

TABLE II

VENOUS PRESSURES OF NORMAL PERSONS BY INDIRECT METHODS

DATE	AUTHOR	POSITION OF PATIENT	METHOD	REFERENCE POINT	RANGE MM. H_2O
1902	Frey[57]	Sitting	Weights on vein to prevent back flow of blood	Hand placed at level of right auricle	10-20 gm.
1902	Von Basch[58]	Sitting	Mercury in glass cylinder	Hand placed at level of right auricle	52-108
1906	Von Recklinghausen[3]	Sitting	Capsule and air	Sternoclavicular joint	20-120
		Supine	Capsule and air	Midway between xiphoid and back	20-120
1906	Sewall[59]	Sitting	Calibrated spring to collapse vein	Level of heart	Average 44
1908	Hooker and Eyster[60]	Sitting	Capsule	Level of heart	40-99
1911	Hooker[61]	Sitting	Capsule	Midway between tip of sternum and back	20-160
1912	Howell[62]	Erect	Pressure at which arm begins to swell	Costal angle	40-130
1913	Barach and Marks[63]	Erect	Capsule	Subcostal angle	80-180
		Horizontal	Capsule	?	35-110
1914	Hooker[64]	Supine	Capsule	Midway between costal angle and back	124-156 day 70-80 night
1915	Clark[65]	At 45° reclining	Capsule	Midway between costal angle and back	50-160
1916	Hooker[66]	At 45° reclining	Capsule	Midway between costal angle and back	190 below 50 yr. 260 above 75 yr.
1918	Brown[67]	Recumbent	Capsule with fluid medium in place of air	Level of heart	30-90
1918	Briscoe[68]	Sitting	Capsule	Subcostal angle	90-120 ♂ 70-110 ♀
1924	White[69]	Sitting	Capsule	Subcostal angle	35-95
1924	Eyster and Middleton[7]	----------	Capsule	----------	10-100
1929	Eyster[12]	Supine	Capsule	Junction of anterior and middle thirds of thoracic diameter	40-60
		Sitting	Capsule	?	40-60
1931	Kastlin and Maclachlan[71]	Horizontal	Capsule and transillumination	Junction of anterior and middle thirds of thoracic diameter	Below 110
1932	Owens[72]	Recumbent	Capsule	?	35-90
		Erect	Capsule	?	Average 90
1932	Kountz, Pearson, and Koenig[13]	Sitting	Capsule with air	Subcostal angle	Below 70
1933	Brams, Katz and Schutz[28]	Horizontal	Capsule and transillumination	Junction of anterior and middle thirds of thoracic diameter	40-135

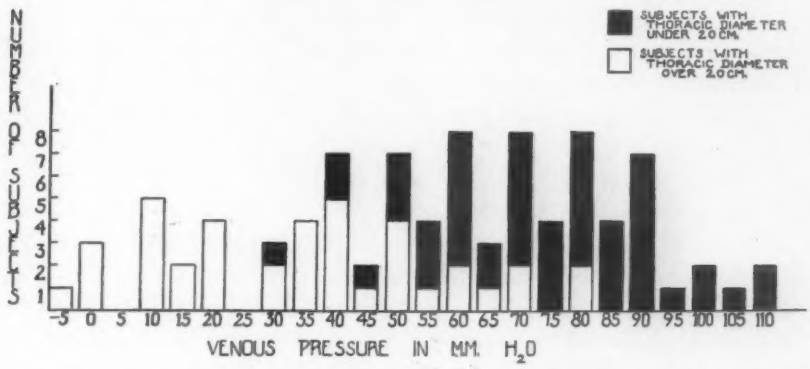
SUBJECTS WITH THORACIC DIAMETER UNDER 20 CM.
SUBJECTS WITH THORACIC DIAMETER OVER 20 CM.
NUMBER OF SUBJECTS
1 2 3 4 5 6 7 8
-5 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110
VENOUS PRESSURE IN MM. H2O

Fig. 3.—Venous pressure measurements in 90 normal subjects using the reference point of Moritz and von Tabora, 5 cm. dorsal to fourth costochondral junction.

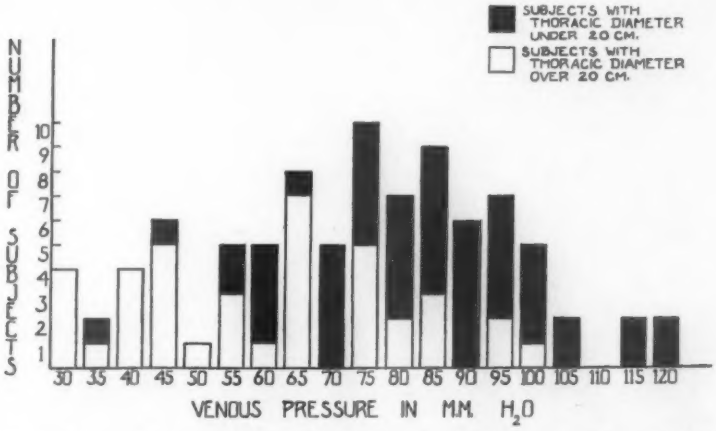
SUBJECTS WITH THORACIC DIAMETER UNDER 20 CM.
SUBJECTS WITH THORACIC DIAMETER OVER 20 CM.
NUMBER OF SUBJECTS
1 2 3 4 5 6 7 8 9 10
30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120
VENOUS PRESSURE IN MM. H2O

Fig. 4.—Venous pressure measurements in 90 normal subjects using the reference point of Eyster, at junction of middle and anterior thirds of thorax.

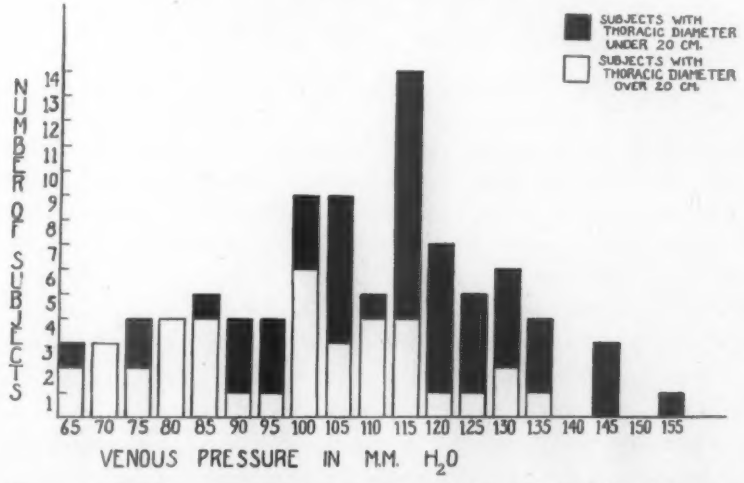
SUBJECTS WITH THORACIC DIAMETER UNDER 20 CM.
SUBJECTS WITH THORACIC DIAMETER OVER 20 CM.
NUMBER OF SUBJECTS
1 2 3 4 5 6 7 8 9 10 11 12 13 14
65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155
VENOUS PRESSURE IN MM. H2O

Fig. 5.—Venous pressure measurements in 90 normal subjects using the reference point of von Recklinghausen, at midpoint of thorax.

gested that the venous pressures found in these persons with large chests are low, not because of an actual change in the venous pressure, but because the shape of the thorax has resulted in the setting of the zero point in a falsely high position. After all, there seems to be little reason to relate the level of the venous reservoir to the front of the chest when the subject is in the supine position. It might be expected that the level of the auricle under these conditions would be more closely related to the posterior boundaries of the thorax, on which the heart lies, than to the anterior thoracic wall to which it is not even firmly attached. As seen in these results, the more the element of the thoracic diameter is minimized in the selection of the reference point, the narrower is the range of venous pressure and the more equitable is the distribution about the mean of the subjects with larger chests.

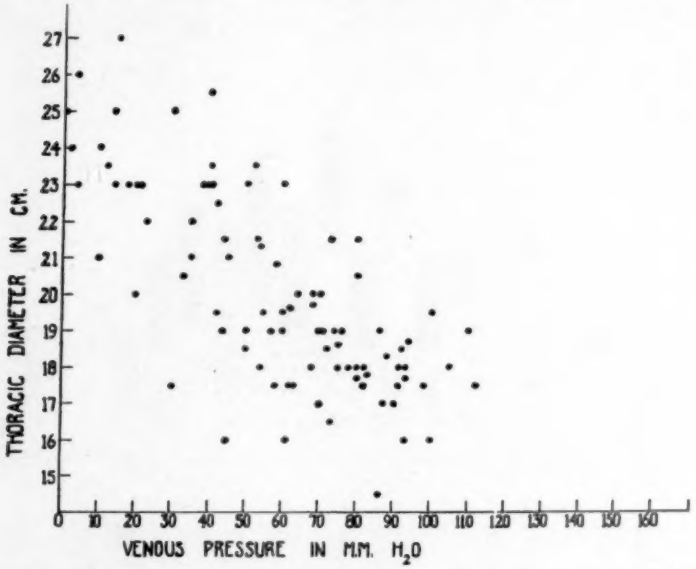

Fig. 6.—Venous pressure in relation to thoracic diameter in 90 normal subjects using the reference point of Moritz and von Tabora.

These considerations led us to eliminate the thoracic diameter in the establishment of the reference point by placing the zero point of the manometer in a constant relation to the level of the table on which the subject was lying. For reasons to be discussed later the point chosen was 100 mm. above the table. When this point was used, approximately 80 per cent of the subjects had venous pressures falling within a 60 mm. range, and there was an equal distribution of the subjects with large chests on each side of the mean pressure (Fig. 7).

The use of a point related to the back of the thorax as a reference point has added to the usefulness of the venous pressure measurement in patients with large chests who showed evidence of mild right-sided

heart failure. With the use of the Moritz and von Tabora reference point, venous pressure measurements in such cases gave values only at the upper limits of normal, but, with the use of a point related to the back of the thorax, the venous pressures were definitely elevated and more nearly in accord with the state of the patient.

In view of the above findings it is suggested that an acceptable reference point should be defined in relation to the posterior surface of the chest rather than in relation to the thoracic diameter or the anterior surface of the chest. To approximate the level of the right auricle, it is suggested that the reference point be set 100 mm. above the skin of the back, i.e., 100 mm. above the table top. This 100 mm. is about the distance from the back to the posterior border of the auricle in the frozen sections of cadavers (see Fig. 1); the distance also compares with the rougher measurements obtained with the aid

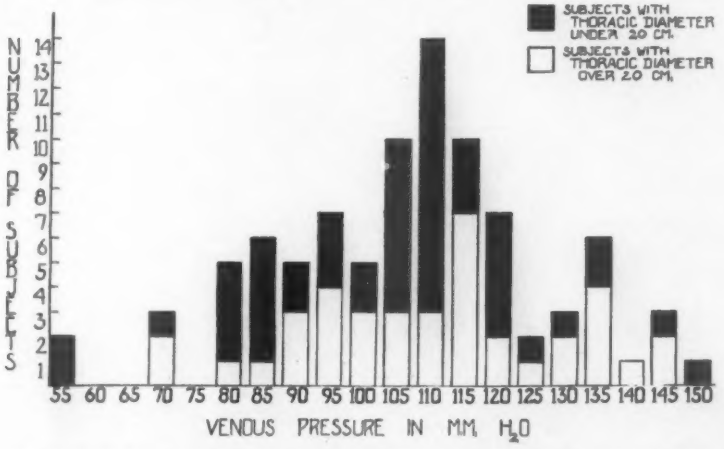
SUBJECTS WITH THORACIC DIAMETER UNDER 20 CM.
SUBJECTS WITH THORACIC DIAMETER OVER 20 CM.
NUMBER OF SUBJECTS
1 2 3 4 5 6 7 8 9 10 11 12 13 14
55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150
VENOUS PRESSURE IN MM. H2O

Fig. 7.—Venous pressure measurements in 90 normal subjects with the reference point in a constant relation to the level of the table—100 mm. anterior to back of thorax.

of the fluoroscope. When this reference point was used, the extreme range of venous pressure of 90 normal subjects was from 50 to 150 mm.; 80 per cent of the readings lay between 80 and 130 mm. This reference point of course is for use only when the subject is in the supine position.*

*Since venous pressure measurements are often desired in patients with severe cardiac failure who are unable to lie flat, an attempt was made to compare venous pressure in the supine position with the pressure in the 45-degree reclining and 90-degree sitting positions. In the upright positions the reference point and the site of venipuncture were placed at the level of the fourth costochondral junction. Fifty normal subjects were studied in this manner. The range of venous pressure is from 20 to 105 mm. in the 45-degree reclining position and from 40 to 135 mm. in the 90-degree position. These ranges are not very different from those observed in the supine position, but in a given individual there was no apparent relation between the level of venous pressure in one position and that in the other. The lack of relation was marked in some patients with heart failure who had abnormally high venous pressures in the supine position but often had venous pressures within the presumed normal range in the upright positions. Because of the absence of relationship between the venous pressure in the supine and upright position in normal subjects and the disparity in the venous pressure levels in these positions in cases with congestion, it seems, in the present state of our knowledge, that measurements of venous pressure in different positions of the body cannot be directly compared.

Figs. 8 and 9 are presented to show the position of the reference point in cross sections of two chests of different diameters. In Fig. 8 the anteroposterior diameter of the thorax is 17 cm. In a chest of such size the position of the reference point is satisfactorily established near the level of the right auricle when either the point 5 cm. posterior to the fourth costochondral junction or that 100 mm. anterior to the top of the table is used. In chests of larger size, as in Fig. 9, the reference point 5 cm. posterior to the fourth costochondral junction is in a less constant relation to the auricle than when a point

Fig. 8.

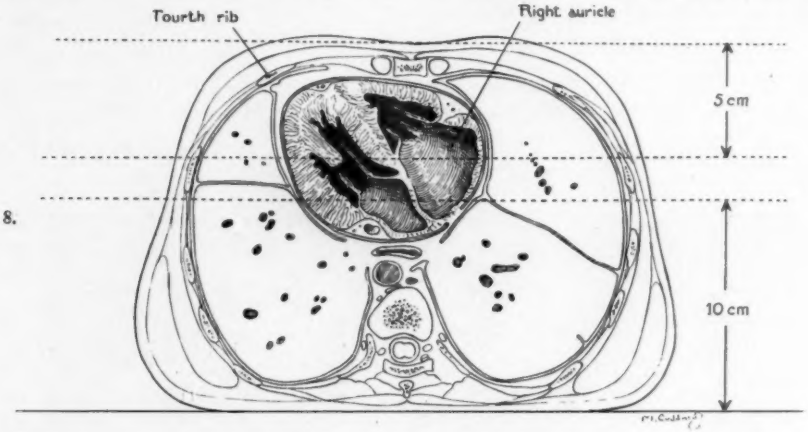

Fig. 9.

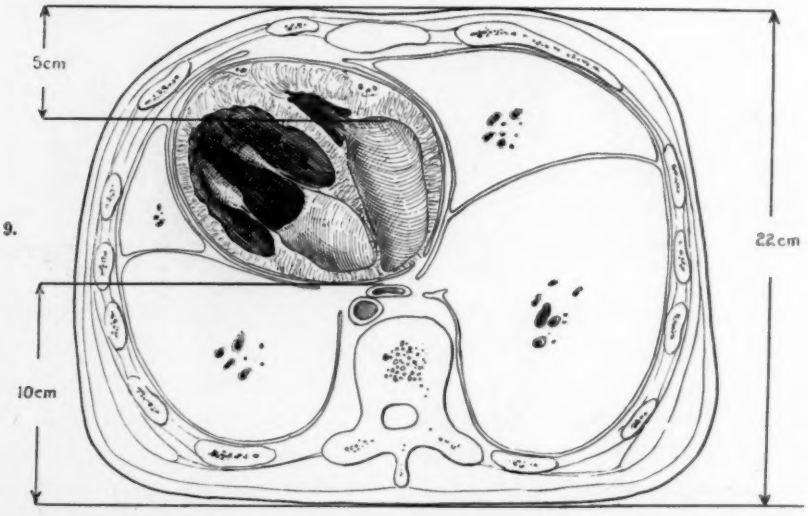

Fig. 8.—Cross section of cadaver redrawn from Eycleshymer and Schoemaker. Thoracic diameter, 17 cm. With this thoracic diameter all the reference points in common use are near the level of the right auricle.

Fig. 9.—Cross section of cadaver. Thoracic diameter 22 cm. With this thoracic diameter the level of the reference point of Moritz and von Tabora is at the upper border of the right auricle.

100 mm. anterior to the back is used. The observations under the fluoroscope and on cadavers indicate that in adults the thickness of the vertebrae and other structures posterior to the heart is less variable than the thoracic diameter in the same patients. This observation is the basis for the selection of the reference point 100 mm. anterior to the back of the chest. It is to be expected that in young children the bony structure is so much smaller that a different reference point will be required. No attempt has been made to study this aspect of the problem.

The usefulness of a reference point which is not displaced by variations in the thoracic diameter is illustrated by Fig. 10. This is a lateral view of the chest of an emphysematous patient in the supine

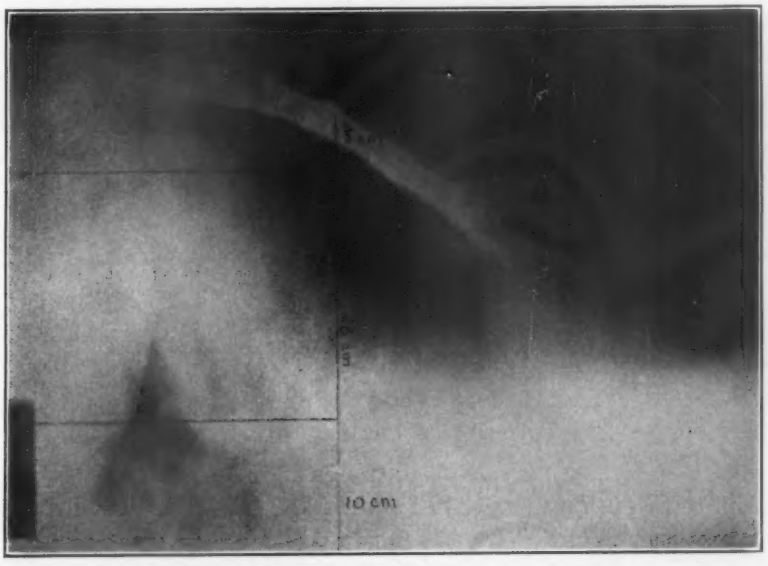

Fig. 10.—Lateral view of subject in supine position. The thoracic diameter at the fourth costochondral junction is 28 cm. This illustrates the failure of the reference point of Moritz and von Tabora to approximate the level of the auricle in subjects with deep chests.

position. The anteroposterior thoracic diameter was 28 cm. The reference point of Moritz and von Tabora places the zero point of the manometer at or near the level of the apex of the heart. On the other hand, a level 100 mm. above the table top closely expresses the position of the right auricle. In such an individual the venous pressure as measured by the method of Moritz and von Tabora could be elevated at least 130 mm. before it reached an abnormal value.

TECHNIQUE SUGGESTED FOR MEASUREMENT OF VENOUS PRESSURE

On the basis of the observations here reported, a standard modification of the Moritz and von Tabora method of measuring venous pressure is suggested, as follows: The apparatus of Moritz and von

Tabora is used, selecting manometer tubing of 2 mm. bore and a needle of gauge 16 to 20. The subject lies quiet and relaxed in the supine position for ten minutes or more before the measurement is attempted. The arm (the measurement is made in an antecubital vein) is abducted to 45 degrees and supported comfortably on a pillow so that the site of venipuncture is below the level at which the veins tend to collapse (this is usually about the middle of the chest; presumably in subjects with thick chests it may be nearer the back). The zero point of the manometer should be set 100 mm. above the level of the back, i.e., 100 mm. above the table on which the patient lies (Fig. 1).

A tourniquet may be used to facilitate entry into the vein. When the needle enters the vein, the tourniquet is released and salt solution is run into the vein to wash the syringe and needle free of blood. Repeated readings are then made of the level of the fluid in the manometer over a period of several minutes until an essentially constant level of pressure is attained.

SUMMARY

The observations reported in this paper have dealt with some of the factors influencing the measurement of venous pressure by the direct method. They indicate that errors may be introduced (a) by certain variations in the technique, including:

(1) the level of the site of venipuncture, and
(2) the degree of abduction of the arm;

and (b) by certain variations in the state of the patient, including his position, relaxation, and type of respiration. Modifications of current techniques are suggested which tend to minimize these errors.

Moreover, the evidence from anatomical material and from roentgenologic measurements indicates that the methods now used for establishing the level of the auricle may, in persons with deep chests, tend to place the assumed level of the auricle at a falsely high position. This, in turn, leads to a falsely low venous pressure reading. To minimize this error a new method of establishing the reference point is suggested, a method which relates this point to the posterior rather than the anterior surface of the chest. Anatomical evidence indicates that in adults in the supine position the level of the auricle is approximately 100 mm. anterior to the skin of the back. When this level is used as the reference point, variations in chest diameter are not reflected in the venous pressure readings.

The range of venous pressures in normal people in the supine position, using a reference point 100 mm. anterior to the skin of the back, is from 50 to 150 mm. of water.

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UNUSUAL FORMS OF RHYTHMS INVOLVING THE A-V NODE*

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PERSISTENT auriculoventricular rhythm is a rare condition and usually is diagnosed only by means of the electrocardiograph. A survey by Dr. H. A. Kaplan has shown that there were only twenty-four cases in the last 7000 patients' records in our files. Nodal escape and temporary shifting of the pacemaker to the A-V node have been noted to be more common than permanent nodal rhythm. In the past two years we have seen four cases of atrioventricular rhythm which are unusual.

I. RECIPROCAL RHYTHM FOLLOWING STIMULATION OF THE CAROTID SINUS

Although reciprocal rhythm has been described on numerous occasions[1-13] and ascribed to vagal hypertonicity,[9-10] we know of no recorded instance in which it was produced by reflex stimulation, and in which the differentiation from the closely resembling condition of sinus bradycardia, nodal escape, and interference dissociation[14-19] could be made in the same patient. This we have been able to demonstrate in the case which we are reporting. This patient suffered from dizziness, fainting spells, and epileptiform convulsions which could be reproduced by carotid sinus pressure, indicating a hypersensitive carotid sinus mechanism. This was further substantiated by the fact that atropine sulfate relieved the spontaneous attacks and prevented the attacks following carotid sinus compression.

Electrocardiograms (Lead II) taken during carotid sinus pressure (left side) showed on one occasion (Fig. 1) the development of sinus bradycardia (with a shifting pacemaker), a series of nodal escapes, interference dissociation, and once ($R_{10} - P_8 - R_{11}$) a pseudoreciprocal rhythm. On another occasion (Fig. 2) carotid sinus pressure (of both sinuses simultaneously) produced sinus bradycardia, a series of nodal escapes with some retrograde P-waves (P_5, P_6, P_8, P_{19}, P_{20} and P_{21}), and true reciprocal rhythm ($R_6 - P_6 - R_7$, $R_{21} - P_{19} - R_{22}$, and $R_{23} - P_{20} - R_{24}$).

Analyzing Fig. 1 in more detail, it will be seen that following carotid sinus pressure there occurs a shift in the pacemaker (P_5) associated with a prolongation of the P-R interval from 0.16 to 0.20 second, followed by escape of the A-V node with sinus beats interspersed. The QRST complexes of the nodal beats differ in contour from those of the

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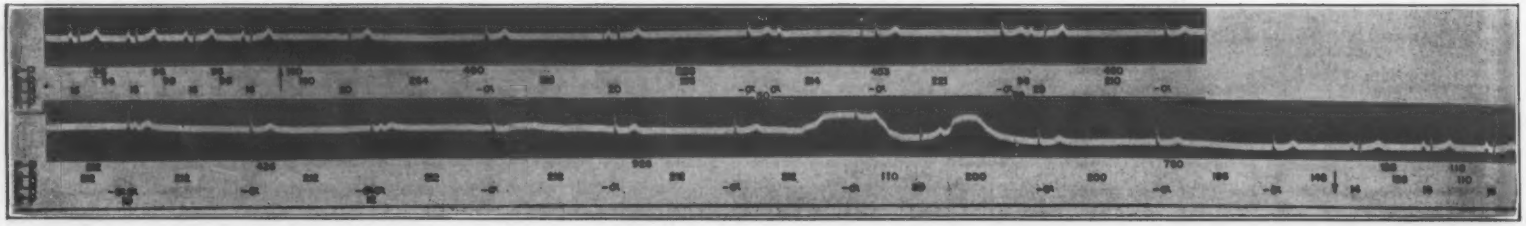

Fig. 1.—Continuous electrocardiographic record (Lead II) showing effect of pressure on left carotid sinus begun at upright arrow and ended at inverted arrow. All the P- and R-waves are labelled sequentially; below the curve are given the R-R, P-P, P-R and in some beats the R-P intervals in 100 times their value in seconds. $\propto$ and $-\propto$, respectively, indicate absence of A-V conduction from auricle to ventricle and vice versa. Discussed in text. In Figs. 1 and 2 the reduction in reproduction may make it advisable to use a hand lens.

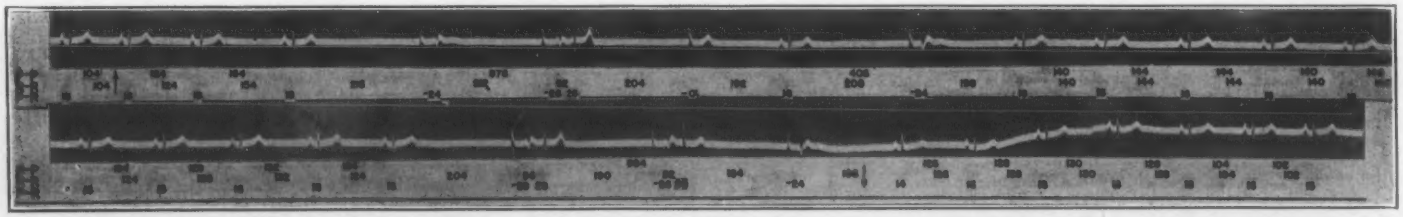

Fig. 2.—Continuous electrocardiographic record (Lead II) showing effect of pressure on both carotid sinuses begun at upright arrow and ended at inverted arrow. Conventions as in Fig. 1. Discussed in text.

sinus beats and differ slightly from each other. As the carotid sinus pressure is continued, the rate of the nodal pacemaker accelerates, i.e., the first nodal escape, R_6, comes after an R-R interval of 2.64 seconds, and the last (R_{23}) before the carotid sinus compression was relaxed occurred after an R-R interval of 1.96. During this period of nodal beats sinus P-waves are seen (e.g., P_6, P_7, P_8, P_9, P_{10}, and P_{11}), some of which are conducted and interrupt the nodal rhythm (e.g., P_6, P_8, and P_{11}); the others are blocked, presumably because they reached the node during its absolute refractory period, i.e., at intervals of 0.50 second, or less, after the nodal beat. P_8, however, occurs 0.68 second after the nodal beat R_{10} and is conducted, simulating reciprocal rhythm. That this is not reciprocal rhythm is shown by the resemblance of P_8 to the other sinus P-waves.[6, 20] In this instance there is retrograde conduction block, as no nodal beat has invaded the auricle.[6, 8, 21]

The conditions illustrated in Fig. 2 are entirely different. Here, carotid sinus pressure causes a slowing of the rate of discharge of the sinus node, e.g., P_3, P_4, P_7, P_9 to P_{18}, P_{22} to P_{26}. Whenever the slowing of the sinus node becomes excessive, as between P_4 and P_7, between P_7 and P_9, and between P_{18} and P_{22}, the A-V node escapes. The nodal beats differ from those shown in Fig. 1, except only R_8, in that there is retrograde conduction giving rise to P-waves (e.g., P_6, P_8, P_{19}, P_{20}, P_{21}) totally different in contour from the sinus P-waves. The R-P intervals of these retrograde P-waves vary from 0.28 second to 0.24 second. In every instance in which the R-P interval is longer than 0.24 second the retrograde P is conducted back through the A-V node, giving rise to a second ventricular complex. However, the retrograde P-waves having an R-P interval of 0.24 second are not conducted back into the ventricle. Apparently the path for auriculoventricular conduction in this instance is refractory when the R-P interval is 0.24 second, but not when the intervals are longer. It is interesting to note that the second ventricular complex of the reciprocal rhythm shows varying degrees of aberrant conduction.

This experience serves to emphasize the fact that reciprocal rhythm should be sharply differentiated from "pseudoreciprocal" rhythm, which resembles it closely, but which is a phenomenon of interference dissociation. Reciprocal rhythm should be diagnosed only when the P-wave between the two ventricular beats differs considerably from the sinus P-waves.[6, 20] This has not always been done in the past. This mechanism is of little practical significance, but it is important in demonstrating the possibility of two-way conduction in quick succession through the A-V node. This is doubtless due to the fact that the path for forward conduction is not the same as that for retrograde conduction. In a dense meshwork of fibers such as occurs in the A-V node, this functional split into more than one conducting path is not difficult

to conceive.[22] The rarity of reciprocal rhythm even when compared to retrograde conduction shows that this split in conduction pathways is unusual indeed. Reciprocal rhythm is one example of the re-entry phenomenon.

II. VARIATIONS IN P-R INTERVALS IN NODAL RHYTHM

In the case of reciprocal rhythm described above there were variations in the R-P interval. Recently, we have seen two other somewhat similar cases (Figs. 3 and 4). In both it will be noted that the R-R interval is constant, while the R-P or P-R interval varies and with it the P-P interval. There are two possibilities to consider in such cases:

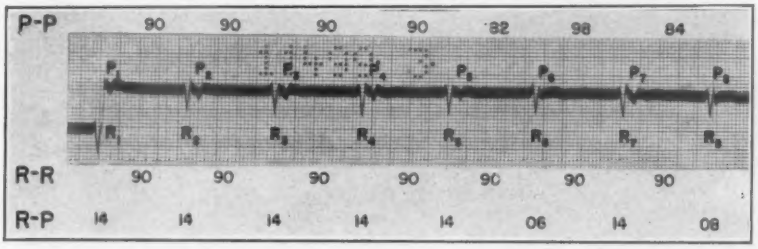

Fig. 3.—Electrocardiographic record (Lead III) showing variations in P-R interval in a case of nodal rhythm. Since in all the beats R precedes P, the P-R interval is given as R-P. Conventions otherwise as in Fig. 1. Discussed in text.

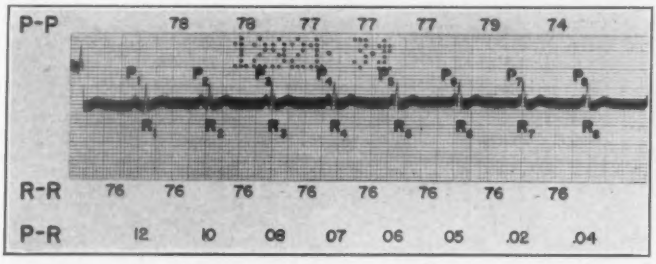

Fig. 4.—Electrocardiographic record (Lead II) showing variation in P-R interval in a case of nodal rhythm. Conventions as in Fig. 1. Discussed in text.

(1) a shift in the nodal pacemaker or (2) variation in the retrograde conduction. In these cases we are inclined to the view that the variability of the P-R (R-P) interval is due to the second mechanism, since there are no variations in the R-R intervals such as would be expected if the former were true. It is well known that forward conduction through the A-V node occurs with greater facility than retrograde conduction, and it is therefore understandable that the latter will be more susceptible of variation than the former. The possibility that we are dealing with sinus arrhythmia and simultaneous nodal rhythm with interference dissociation is ruled out, we believe, by the fact that in both of these patients the other leads show nodal rhythm with constant P-R (R-P) intervals.

III. SHORT P-R INTERVAL ASSOCIATED WITH LENGTHENED QRS INTERVAL

A number of reports have appeared dealing with records of short P-R intervals associated with lengthening of the QRS interval.[23-27] It was concluded that this condition is more benign than other forms of intraventricular block and is probably not a sign of heart disease. While Wolf, Parkinson, and White[24] ascribed it to functional intraventricular block due to abnormal spread through the junctional conducting tissue and ventricles, Wolferth and Wood[23] attribute the phenomenon to early arrival of the impulse to the ventricle via the bundle of Kent

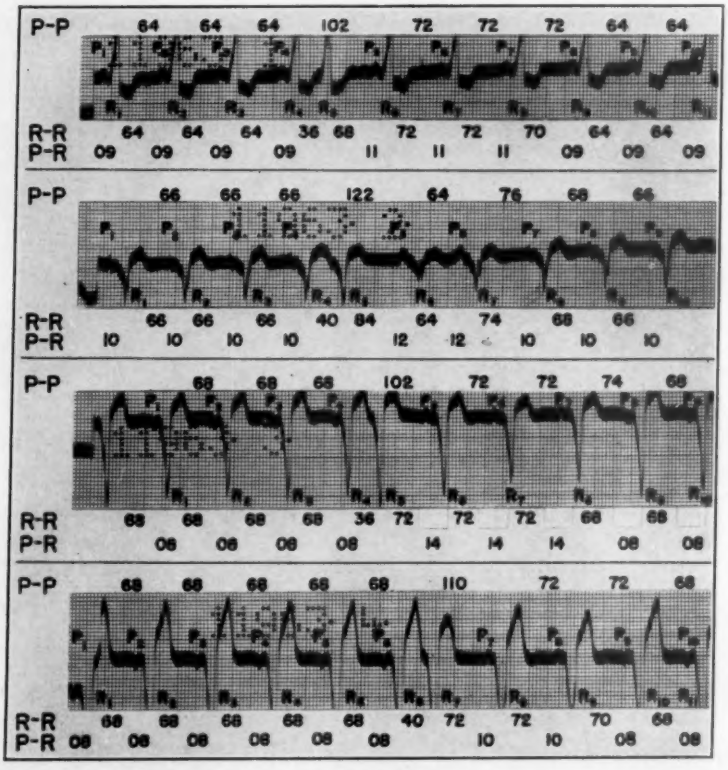

Fig. 5.—Electrocardiographic record (all four leads; fourth lead is CF_3 American Heart Association classification) showing an unusual instance of transient shortening of P-R interval in a case of organic intraventricular block. Conventions as in Fig. 1. Discussed in text.

(located at the junction between right auricle and ventricle), thereby making the spread through the ventricles abnormal. In many cases the disappearance of the condition spontaneously or with atropinization causes the P-R interval to lengthen as the QRS interval shortens. However, this was not true in one of Tung's cases.[26] We have recently seen an instance of short P-R interval and long QRS interval in a patient with severe cardiac damage caused by coronary sclerosis. In this patient ventricular premature systoles caused changes in the P-R interval without abolishing the intraventricular block. The record is shown in Fig.

5. The change in the P-wave contour and in the P-R interval following the extrasystoles is readily seen (as well as the associated change in QRS contour). The interpretation in this case, we believe, is of intraventricular block of the common bundle branch variety associated with an upper nodal rhythm, reverting at times to the sinus node or to another focus in the A-V node. The intraventricular block is persistent regardless of where the impulse arises, and in this case has the same prognostic significance as intraventricular block with normal P-R intervals. It is difficult to conceive that, in this case, we are dealing with spread through the bundle of Kent, and consequently we question this interpretation in other instances. It is possible to produce a shift in the pacemaker to the A-V node with a consequent shortening of P-R interval either when the sinus node is diseased or depressed by vagus stimulation. Under such circumstances it is conceivable that the impulse may spread through a preferential path[25] in the junctional conduction tissue since the disease affecting the sinus node, or the vagal depression, may also affect the A-V junctional tissue. Aberrant conduction is not uncommon in nodal escape, and it is highly probable that this may on occasion be severe enough to simulate organic intraventricular block. When the pacemaker reverts to the sinus node the spread through the ventricles may become normal again or, as in our case, may persist. It is unnecessary in view of these circumstances to postulate spread over the hypothetic bundle of Kent. In upper nodal rhythm it has been shown[15, 28, 29, 30] that the P-wave often does not differ remarkably from the sinus P since the auricular spread in both is of a similar pattern, the only difference being the shortened P-R interval.

SUMMARY

Several unusual electrocardiograms illustrating different forms of A-V rhythm have been described:

1. A case in which, with carotid sinus hyperirritability and reflex stimulation, the differentiation of reciprocal rhythm and the closely resembling condition of sinus bradycardia, nodal escape and interference dissociation with pseudoreciprocal rhythm could be demonstrated.

2. Two electrocardiograms which showed variations in the P-R (R-P) interval, but in which the R-R interval remained constant.

3. One electrocardiogram which showed a short P-R interval and a prolonged QRS complex, with a shift in the pacemaker to the S-A node following an ectopic ventricular beat, from a patient with severe chronic cardiac disease.

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CORONARY OCCLUSION, HEART FAILURE, AND ENVIRONMENTAL TEMPERATURES*

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RECENT discussion concerning seasonal variation in the frequency of attacks of coronary occlusion has emphasized the need for more complete knowledge of the relation of environmental temperatures to coronary thrombosis and heart failure. There has been a feeling that the increased frequency of acute infections during winter largely accounts for the higher heart failure and cardiac death rates of that season. Infections, particularly of the respiratory tract, undoubtedly do enter into the increased winter hazards for patients of limited cardiac capacity. But there seem to be, we believe, other important factors at work, factors of a general metabolic nature not usually taken into consideration by cardiologists.

There is in the medical literature no careful study of the onset of noninfectious cardiac failure of various kinds which was made to ascertain whether there be any seasonal fluctuation of statistical significance. For these reasons we have undertaken the study of the problem along two lines of approach. First, we have obtained from the literature reports of large series of cases of coronary occlusion which included information as to the months in which the acute attacks occurred. This has been supplemented by material from the autopsy records in this hospital. Second, we have studied the seasonal factor in the records of all patients with noninfectious cardiac failure who were admitted to the Cincinnati General Hospital from Jan. 1, 1920, through Dec. 31, 1937.

CORONARY OCCLUSIONS AND SEASON

Recognition of the clinical entity of coronary thrombosis and infarction of the heart has become so widespread in the last two decades that adequate data may be collected from the medical literature to ascertain whether any relationship exists between season and acute attacks. Therefore, we have studied published reports with information on this subject and autopsy cases occurring in the Cincinnati General Hospital from 1922 through 1936.

The first reference to any relationship between season and acute attacks of coronary thrombosis appeared in a paper by Wolff and White,[1] in 1926, in which they observed that "most of the cases of coronary thrombosis in New England occur in the winter." Acute coronary

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occlusion in all but one of their twenty-three autopsy cases occurred between October and April, inclusive. The next report was that of Wood and Hedley,[2] in 1935, who found a low summer and high winter incidence in 133 cases in Philadelphia between 1932 and 1934, inclusive. Their series included both private and ward patients. Mullins,[3] in Pittsburgh, analyzed 400 consecutive cases from private, consultation, and hospital practice between July, 1928, and July, 1935. In the 370 in which the date of onset was known, he observed that "almost twice as many initial attacks occurred during December, January, and February, as occurred during the summer months."

By far the largest series was recently reported by Masters, Dack and Jaffe,[4] who collected 612 cases from private, hospital, and consultation practice. Although they noted a higher incidence in December and January, they did not believe that season was important in determining the incidence of acute attacks. This conclusion has been questioned, however, by Rosahn,[5] who used their statistics. Later in the same year one of us[6] reported that in 247 autopsy cases from the Boston City Hospital between 1906 and 1936 there was a low incidence of acute attacks in the summer months. There was a slightly larger number in the spring than the winter.

The time of onset of acute attacks in patients coming to autopsy in the Cincinnati General Hospital from 1922 through 1936 could be ascertained in 278 instances in 8,673 consecutive autopsy records. A number of records were rejected because of lack of information regarding the time of onset. The data as to month of onset of these 278 attacks are included in Fig. 1 and Table I, and reveal the same decline from winter to summer as is seen in all the other observations reported.

TABLE I

DISTRIBUTION BY MONTHS OF ACUTE ATTACKS OF CORONARY OCCLUSION

	JAN.	FEB.	MAR.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	TOTAL
Master (New York City)	75	43	48	48	56	44	54	50	46	46	39	63	612
Mullins (Pittsburgh)	36	50	31	28	27	29	24	18	26	29	37	35	370
Present series (Cincinnati)	33	27	25	22	23	13	19	10	22	25	33	26	278
Bean (Boston)	20	18	26	29	20	13	11	11	28	19	25	27	247
Wood and Hedley (Philadelphia)	19	13	8	7	11	1	7	4	15	14	19	15	133
Total	183	151	138	134	137	100	115	93	137	133	163	166	1640

In order to make a comparison of these five groups the number of acute attacks by month was corrected on the basis of a thirty-one-day month. The equalized curves of incidence are found in Fig. 1, in which the percentage of each group occurring month by month is

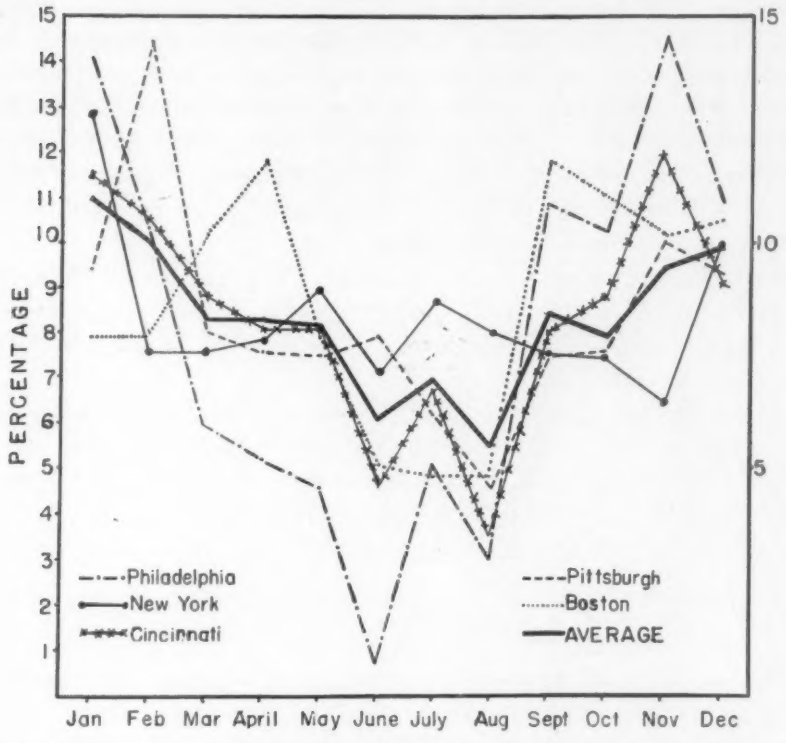

Fig. 1.—Percentage of attacks of coronary occlusion by month corrected on the basis of a thirty-one-day month.

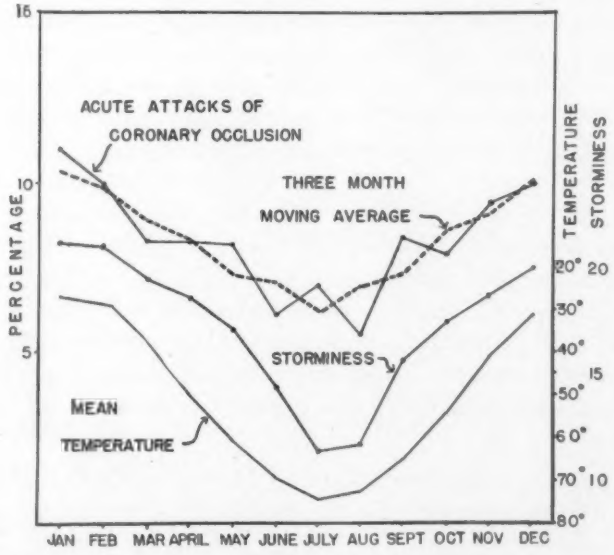

Fig. 2.—Percentage of attacks of coronary occlusion by month compared with mean temperature and storminess.

indicated. The heavy line was obtained by using the entire 1,640 cases, also corrected on the basis of a thirty-one-day month. There is here a high winter and low summer level in the curves from each of these cities. From Table I it can be seen that in January 183 acute attacks occurred, whereas in August there were 93, approximately half of that number. This leaves no doubt that in the regions studied acute episodes of coronary occlusion are considerably more frequent in the winter than in the summer months.

Such chance factors as seasonal variation in population shifts or hospital admissions have been considered negligible in the autopsy material, and because of the different sources of the data we do not believe such factors to be significant.

In Fig. 2 the curve for seasonal incidence of acute attacks has been compared with the mean temperature curve (inverted) and storminess.* The similarity of these curves is at once apparent and strongly suggests that fluctuations in temperature and storminess are related to the events culminating in acute coronary thrombosis.

SEASONAL AND PERIODIC ANNUAL VARIATIONS IN FREQUENCY OF NONINFECTIOUS HEART FAILURE

We next present the picture of noninfectious heart failure in its seasonal variations at Cincinnati. Examination was made of all case records of cardiac patients admitted to the Cincinnati General Hospital from Jan. 1, 1920, to Dec. 31, 1937, and selection made of only those patients admitted in evident heart failure not complicated by infection or other external precipitating events such as injuries, burns, or operations. Cases were included when there was constant edema of the ankles or breathlessness at rest sufficiently severe to incapacitate the patients. Although the degree of failure must have varied, the great majority of the patients admitted were acutely ill. Cases in which failure was initiated or accompanied by acute infection of any kind were discarded, as were those in which the oral temperature was over 100° F. on admission, even though localizing signs of infection were not always found. Records of patients hospitalized within the previous three months were discarded in order to include only those whose heart failure was new. Therefore, those included in our presentation represent, as nearly as we were able to ascertain, patients in whom none of the usually encountered external precipitating causes of cardiac failure were present.

Table II presents the detailed grouping of the onsets and admissions on a seasonal basis, separated according to the organic basis of failure. In the arteriosclerotic group we have included all cases of coronary artery disease, hypertension, or both. A few patients in whom the

*By storminess is meant the day to day changeableness of the temperature, as represented in Figure 4 by mathematical coefficients of variability.

organic basis of the failure was uncertain were included in the group with arteriosclerotic heart disease. By syphilitic heart disease we mean that type associated with aortitis and aortic regurgitation. Adjustment to a thirty-one-day monthly basis was made and three-month moving averages were used in order to bring out clearly the seasonal trends shown in Fig. 3. Arteriosclerotic failure *admissions* to the hospital reach a peak in March, while *onsets* of these failures are highest in

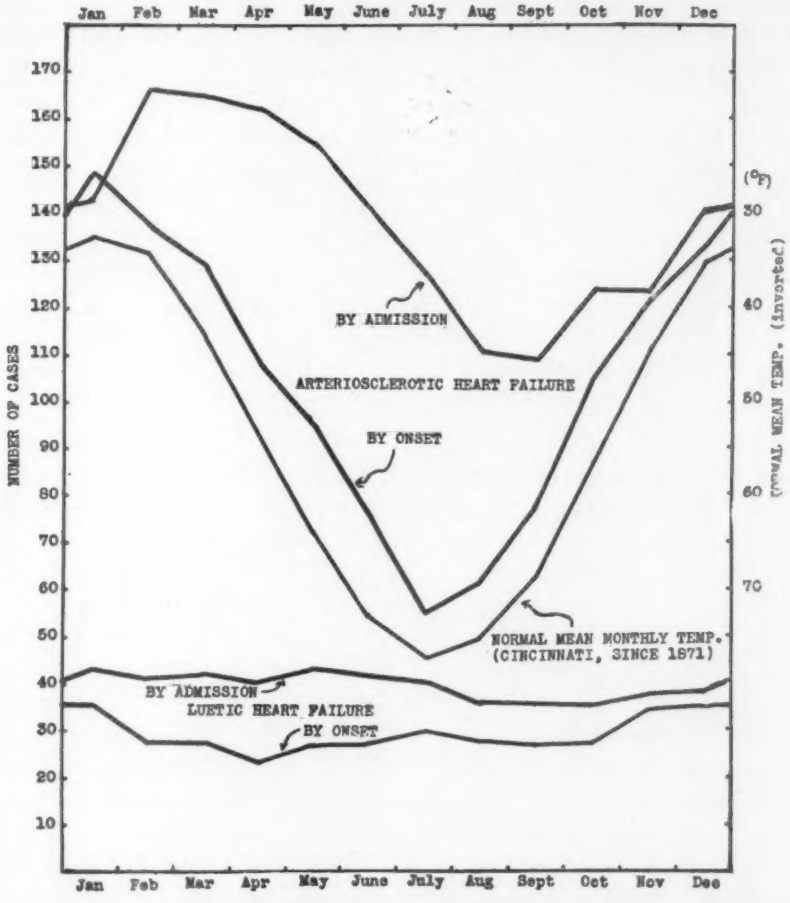

Fig. 3.—Seasonal variation in frequency of heart failure. Actual number of cases equalized to thirty-one-day month basis, smoothed by use of three-month moving average.

February; with the low point of summer a similar one-month lag in admissions is seen. The exceedingly close parallelism between the smoothed onset curve and inverted mean temperature curve for Cincinnati cannot but be of great significance in considerations of the seasonal timing of the failures.

Presumably inactive rheumatic heart disease unaccompanied by fever shows this same seasonal trend in month of onset of congestive failure.

TABLE II

HEART FAILURE ADMISSIONS TO CINCINNATI GENERAL HOSPITAL, 1920-1937, INCLUSIVE (CASES LIMITED AS DESCRIBED IN TEXT)

MONTH	ARTERIOSCLEROTIC			SYPHILITIC			RHEUMATIC	NORMAL
	ACTUAL NO. FAILURES	31-DAY MONTH BASIS	3-MO. MOVING AVERAGE	ACTUAL NO. FAILURES	31-DAY MONTH BASIS	3-MONTH MOVING AVERAGE	ACTUAL NO. FAILURES	MEAN MONTHLY TEMPERATURE CINCINNATI
Failure Onsets by Month								
January	132	132	148	27	27	35.7	13	32.5° F.
February	157	172	137	27	30	27.7	12	34.2° F.
March	108	108	129	26	26	27.3	17	43.1° F.
April	105	108	108	25	26	23.3	5	53.7° F.
May	107	107	95	18	18	26.3	14	64.0° F.
June	67	69	76	34	35	27.0	10	73.0° F.
July	53	53	55	28	28	29.7	9	77.1° F.
August	42	42	61	26	26	27.3	11	75.1° F.
September	89	89	77	27	28	26.3	11	68.8° F.
October	101	101	105	25	25	26.7	20	56.8° F.
November	120	124	121	26	27	34.0	26	44.6° F.
December	139	139	132	50	50	34.7	22	35.1° F.
Failure Admissions by Month								
January	159	159	143	37	37	43.2	23	
February	140	154	166	46	50	41.2	15	
March	186	186	165	36	36	42.3	24	
April	149	154	162	39	40	40.1	22	
May	145	145	155	44	44	42.9	16	
June	162	167	141	43	44	41.8	21	
July	112	112	127	37	37	40.1	13	
August	103	103	111	39	39	36.0	24	
September	115	119	109	31	32	35.7	23	
October	106	106	123	36	36	34.3	23	
November	140	145	123	34	35	37.7	19	
December	117	117	140	42	42	38.0	26	

Although the number of cases is small, we see in Table II that 104 occurred during the colder half of the year, and only 60 during the warmer six months. Syphilitic heart disease, however, shows only a very slight seasonal trend in congestive failure onset, and no significant trend in time of admission.

The seasonal curve of arteriosclerotic heart failure persists if cases be grouped by either race or sex, and is thus a quite general finding. Failures in this group occurred at considerably earlier ages in the colored than in the white race, and slightly earlier in women than in men, but the seasonal relationships of failure onset remain uniform in all groups.

On quite a different basis the decline in frequency of heart failure with rising warmth stands out from our study. Whole years of warmth, particularly when the warmth came in winter months, have been associated with an even sharper drop in frequency of nonsyphilitic heart failure than has the summer period of each year. Fig. 4 shows the striking fall in failure frequency in the arteriosclerotic and rheumatic groups that came with the prolonged period of record warmth beginning late in 1929. The number of failures in syphilitic heart disease again failed to decrease with this warmth, just as they failed to decline in the summer season.

During the period covered by our data (1920-1937, inclusive), total admissions to the medical service and heart failures of the type we have selected increased along roughly parallel courses except during the pronounced and prolonged warmth that began late in 1929. With this world-wide warmth, arteriosclerotic and rheumatic heart failure admissions dropped sharply, while no significant change occurred in the syphilitic rate. The abrupt high peak in failures in the arteriosclerotic group for 1933 may be due in part to the sudden work load placed on the relief population, from which a large share of the hospital admissions come, by the substitution of Civil Works Administration work relief for the previous direct food and cash dole. Some histories of our cardiac patients for that period record that the functional breakdown occurred shortly after the patient went to work.

Probably of more importance is the fact that during the years 1930, 1931, and 1932, the greater part of the annual excess warmth came to ameliorate winter cold. The winters of 1930-31, 1931-32, and 1932-33 were unusually mild and without storms, with shrubs and flowers blooming throughout the winter. From the summer of 1933 on, however, the winters returned more nearly to their normal level of temperature and storminess, while the excess warmth came largely in the summer seasons. Again in the first quarter of 1937, however, marked unseasonal warmth and calm lessened the severity of that winter. This may well have been an important factor in the unusually good health that pre-

vailed during and subsequent to the flood period and may have been somewhat responsible for the sharp reduction in both total and heart failure admissions to the hospital in 1937.

Another contributing factor of considerable importance in accounting for the reduction in arteriosclerotic and rheumatic heart failures from late in 1929 to the beginning of 1933 may well have been the reduced physical work load on the unemployed. From 1933 on, as work relief largely supplanted direct dole, heart failures resumed more nearly their former proportion of total admissions. If the load of physical labor were of paramount importance in determining heart

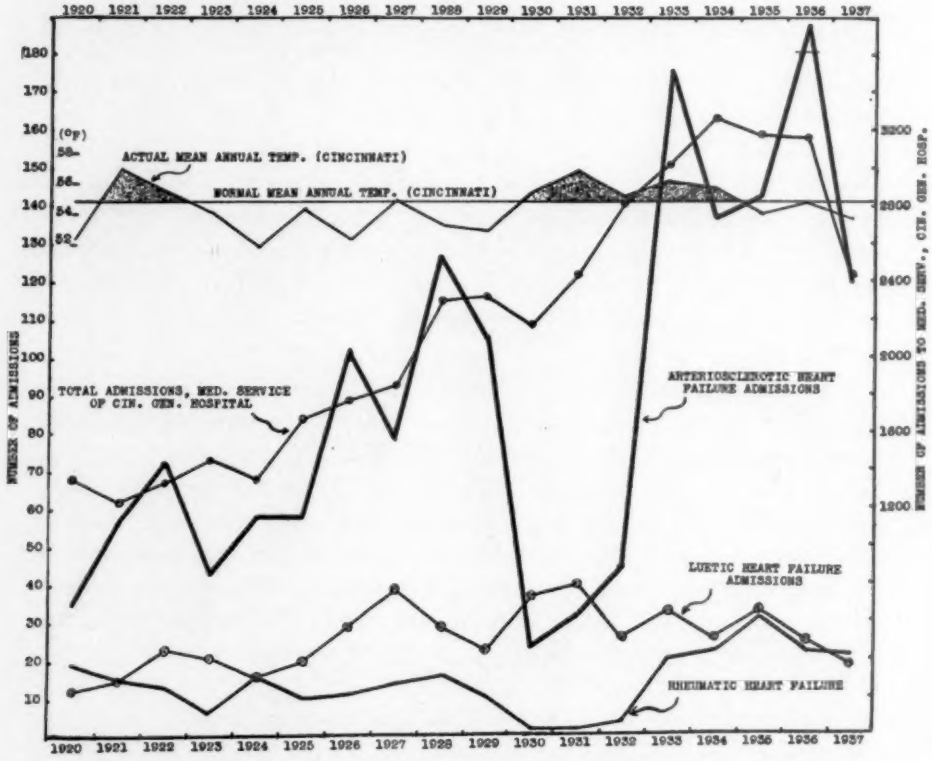
1920 1921 1922 1923 1924 1925 1926 1927 1928 1929 1930 1931 1932 1933 1934 1935 1936 1937
(°F)
ACTUAL MEAN ANNUAL TEMP. (CINCINNATI)
NORMAL MEAN ANNUAL TEMP. (CINCINNATI)
TOTAL ADMISSIONS, MED. SERVICE OF CIN. GEN. HOSPITAL
ARTERIOSCLEROTIC HEART FAILURE ADMISSIONS
LUETIC HEART FAILURE ADMISSIONS
RHEUMATIC HEART FAILURE
NUMBER OF ADMISSIONS
NUMBER OF ADMISSIONS TO MED. SERV., CIN. GEN. HOSP.

Fig. 4.—Variations in annual frequency of heart failure in relation to mean temperature level.

failure, however, failure admissions should have declined more gradually from 1929 to 1933 as employment lessened. Instead, they declined abruptly as the unseasonable warmth came late in 1929.

Little can be said of the brief warm period of 1921-22. Only with the single winter of 1920-21 did the warmth come to relieve the cold of the winter season, and in only one month was this winter warmth accompanied by any marked reduction in storminess. In addition, this period of warmth came while the influenza epidemic of 1918-19 was still considerably in evidence as a factor in cardiac failure.

Several other factors not investigated by us may have been of some importance in accounting for the fluctuations in admissions for failure. Annual irregularities may well have resulted from changes in personnel of the receiving department. It is also remotely possible, although highly improbable, that other hospitals of the city may have admitted greater numbers of patients with heart failure from the indigent population in the period from 1930 to 1932 inclusive, when so few came to the General Hospital. The only other hospital we considered worthy of checking on this point was the Chronic Disease Hospital at the County Home. This hospital was opened late in 1929, before which time inmates of the County Home had been sent to the General Hospital for cardiac failure. In no year since it opened have more than 20 noninfectious heart failure patients in the arteriosclerotic group, or more than 4 in the syphilitic group been admitted, and there was only one patient with rheumatic heart disease in the nine-year period. The yearly average was 8.2 for the arteriosclerotic and 1.6 for the syphilitic groups. The admissions for heart failure were low in both hospitals concomitantly. Thus the opening of the Chronic Disease Hospital did not account for the low admission frequency in 1930-32 at the General Hospital.

Still another factor which might have affected the annual number of patients with heart failure admitted to the hospital has been variations in the number of cardiac patients cared for in the outpatient clinics. The total number of patient visits to the heart clinics each year, however, does not furnish a likely basis for explaining the sudden drop in failure frequency from late 1929 to early 1933. The only interruption in the steady rise of heart clinic visits during the whole period occurred during the warmth of the early depression years, when hospital admissions for heart failure fell off so sharply. And again in 1937 both clinic visits and admissions for failure fell off together. We may, therefore, disregard the outpatient heart clinic activities.

The fact that syphilitic heart disease was not found to be affected significantly by either seasonal or annual warmth is an interesting commentary on this type of heart failure. Here the progress of the incapacitating lesion seems more rapid than with the arteriosclerotic type, so that the slow effects of season are less evident. Many of the case records of syphilitic heart failure showed that there had been repeated admissions at intervals of less than three months, so that only the initial attack is found in our data. The syphilitic process, from first break in compensation to death, usually took about two years, while most of the arteriosclerotic patients carried on considerably longer. Little stress can be placed on the rheumatic heart failure data because of the small number of acceptable cases. Only with their sharp drop in incidence during the warmth of 1929 to 1933 do they provide information of value.

DISCUSSION

The data presented show a marked seasonal swing in the frequency of coronary occlusion attacks. They are almost twice as frequent in winter as in summer. An even greater winter peak is found in the

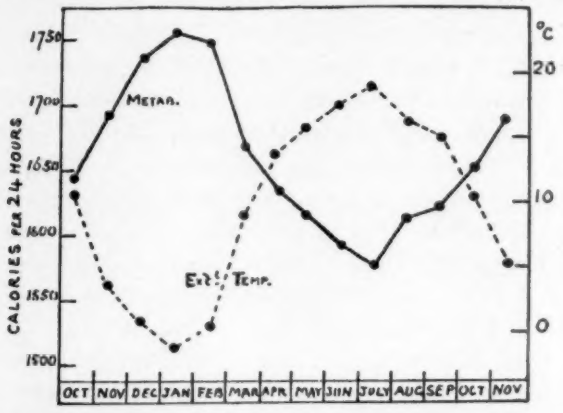

Fig. 5.—Mean monthly metabolism and mean monthly temperature. Gessler (1925), observations on himself. (From Martin, C. J.: Thermal Adjustments of Man and Animals to External Conditions, Lancet 2: 617, 1930.)

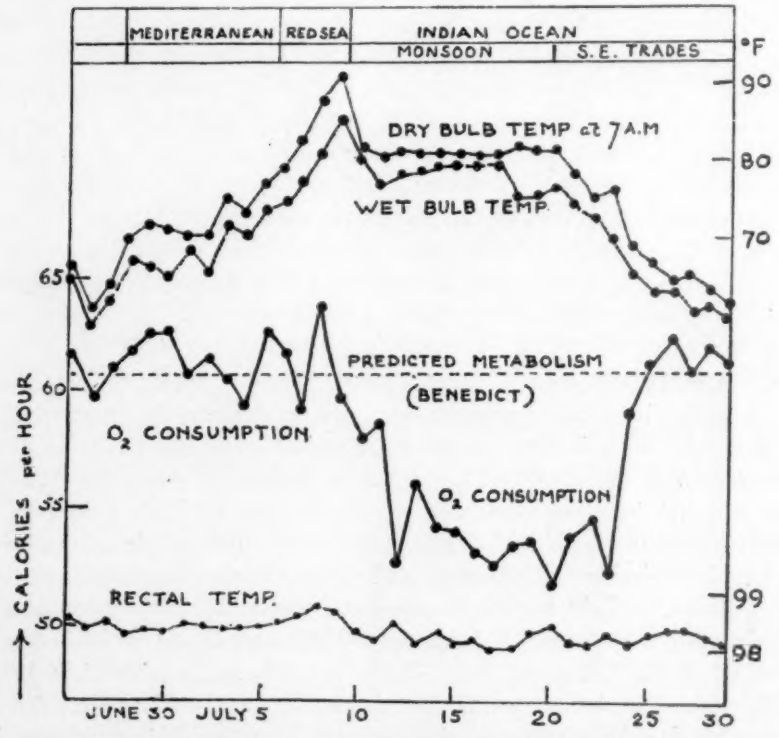

Fig. 6.—Daily observation of basal metabolism of C. J. M. during a voyage from London to Australia, June-July 1923, and daily record of the temperatures of the dry and wet bulb thermometers at 7 A.M. (From Martin, C. J.: Thermal Adjustments of Man and Animals to External Conditions, Lancet 2: 617, 1930.)

frequency of noninfectious arteriosclerotic heart failure onsets, which occurred about two and a half times more frequently in winter than in summer. Just why syphilitic heart failures pursue a course independent of temperature level is not entirely clear. It is probably because of the more rapid course of the disease, with steady progression of the organic lesion.

Explanation of these findings offers great difficulty. A number of possibilities present themselves. It is known that infections, especially of the upper respiratory tract, are most frequent and severe during

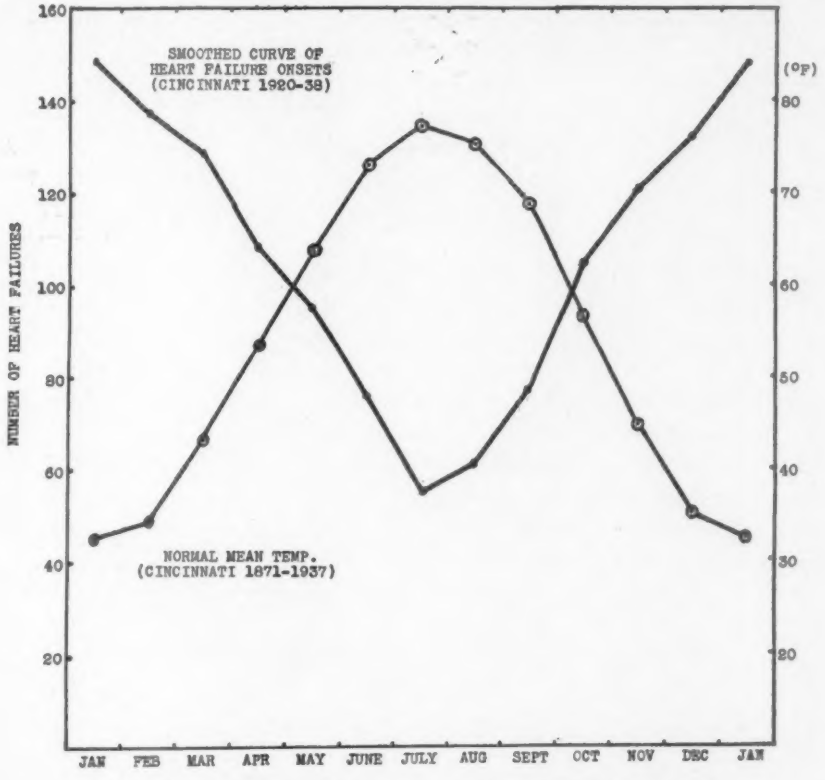

Fig. 7.—Heart failure frequency and mean temperature level.

cold and changeable weather. With these there is a rise in temperature and metabolism, which increases the burden on the heart. When the weather is stormy, fluctuations in temperature may produce a strain by little-known vasomotor reflexes. At least it is known that angina pectoris is likely to be precipitated by walking in cold or windy weather. Certain forms of voluntary activity are also increased in the cold. Such factors increase the burden of the heart and make the life of a cardiac cripple more precarious.

Another factor which may be of fundamental importance is the possible variation of metabolism with change in environmental temperature.

Though a conclusive study of the effect of external environment on metabolism has not been carried out, and though there is no agreement among authorities [Lusk[7]] as to the validity of numerous divergent opinions expressed in the literature, there is an increasing body of evidence on the subject. In Fig. 5 the value obtained on a single individual illustrates a clear inverse relationship between temperature and metabolism [Gessler[7]]. In Fig. 6 are recorded the effects of passage from England to Australia through tropical heat. There are many other reports conveying this same idea for man and animals [Martin[7]]. There is a remarkable similarity between the graphs of Figs. 5 and 7, which show the relation of mean monthly temperature level to oxygen consumption (Fig. 5) and to arteriosclerotic heart failure onsets through the seasons of the year (Fig. 7).

If further evidence is found that external temperature does produce such an effect, it will have an important bearing on the heart failure problem, because it has been shown[8] that the metabolic cost of work performed during activity has a direct relationship to the resting oxygen consumption. The higher the resting metabolic rate, the greater the combustion cost for a given amount of work. The more sluggish individual of the tropics can perform more work on a given amount of combustion than can the more energetic northerner who wastes much of his energy maintaining a higher muscle tone. The northerner can do more work in a unit of time, but he pays a higher price per work unit. As a metabolic machine, he is less efficient.

One of us[9, 10] has discussed the low prevalence of arteriosclerotic and rheumatic heart disease in tropical or subtropical countries as contrasted to their severity in middle temperate regions. The present findings may be taken to support these conclusions. In addition, some metabolic diseases have been found to show a close relationship to climatic and seasonal stress.[11]

SUMMARY

Coronary occlusion attacks are definitely more frequent in winter than in summer in the north temperate regions studied.

In arteriosclerotic and rheumatic patients heart failure is likewise much more frequent in winter cold than in summer warmth; failure onset exhibits a close inverse relationship to mean temperature level in Cincinnati. This group also shows a marked reduction in frequency during warmer and less stormy years, such as came from late 1929 to 1933.

Syphilitic heart failure from aortic insufficiency, however, failed to exhibit any such significant relationship.

Greater frequency of infections and heightened general body metabolism probably act together to increase the winter hazards of existence for cardiac patients, while the calm warmth of summer brings a period of relative safety.

Migration out of northern cold and storms, either temporarily or permanently, is strongly indicated for every patient of limited cardiac reserve whose financial means permit such a course.

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BACTERIAL ENDOCARDITIS SUPERIMPOSED ON SYPHILITIC AORTITIS AND VALVULITIS

A Clinicopathological Study With 5 Case Reports*

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CLINICALLY, it is axiomatic that bacterial endocarditis rarely occurs in an aorta or on an aortic valve previously damaged by syphilis. Pathologic studies have confirmed this. Only five cases in which the existence of such a combination was proved have been reported in the literature up to the present time. The probable pathogenesis has been reviewed by McMillan and Wilbur,[1] Cotton,[2] Briggs,[3] and Bayne-Jones,[4] and will not, therefore, be discussed here.

In a series of 17,000 autopsies at the Los Angeles County General Hospital, 157 cases of vegetative endocarditis were found. Of these there were only 5 cases in which vegetative endocarditis was associated with syphilitic aortitis or valvulitis. Each of these cases presented, in addition, other unusual features. A review of these cases, including clinical and autopsy observations, is herein presented in detail.

Case 1.—Los Angeles County General Hospital, P. F. No. 458-742, Autopsy No. 16964.

E. W., a 61-year-old white sailor, was admitted to the hospital Nov. 11, 1936, with a history of shortness of breath of two years' duration. Otherwise, he had been relatively well until three weeks prior to admission, when he began to have nocturnal dyspnea. One week later he noticed moderate palpitation, and the following week he developed edema of the ankles.

The past history was essentially negative, except for a chancre at the age of 15 years, for which he received no treatment. He denied having had gonorrhea. There had been no serious illnesses and no operations, except a prostatectomy by transurethral resection in 1935.

Physical Examination.—The patient appeared markedly dyspneic and acutely ill. His blood pressure was 175/34; temperature, 97.4° F.; pulse rate, 120; and respiratory rate, 28. The pupils were irregular and reacted very slightly to light, but well in accommodation. There was marked pulsation of the vessels of the neck, with venous engorgement. Examination of the lungs revealed diminished resonance at the bases posteriorly, with many moist râles. His heart was enlarged to the left and downward, and a diastolic murmur was heard at the mitral area. There was a to-and-fro murmur over the aortic area. The pulse was of the Corrigan type. The abdomen was slightly distended, and the liver was palpable three fingerbreadths below the right costal margin. The penis and scrotum were edematous, but otherwise normal. There was marked edema of the lower extremities extending upward

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to the crests of the ilia. Rectal examination revealed a small, hard, nodular prostate. The deep reflexes were absent and position sense was markedly impaired. There was inability to distinguish between dull and sharp.

Laboratory Examination.—The blood Wassermann and Kahn reactions were strongly positive. The hemoglobin was 80 per cent (Sahli); the erythrocyte count, 4,800,000; and the leucocyte count, 8,000, 68 per cent of which were polymorphonuclear leucocytes. The urine was negative except for an occasional granular cast. The orthodiagram showed cardiac enlargement. The aorta was large, but not aneurysmal, and there were calcified plaques in its wall. The electrocardiogram on Nov. 12, 1936, showed left axis deviation and evidence of myocardial and coronary disease. On Nov. 16, 1936, the electrocardiogram was the same except for the occasional occurrence of ventricular extrasystoles. On Nov. 18, 1936, the rhythm had changed to auricular flutter with 2-to-1 block. On Nov. 23, 1936, sinus rhythm was again established. There were changes in the S-T segment in Leads I and III which were suggestive of coronary occlusion, but were not considered diagnostic in view of the complete digitalization.

Progress.—His condition remained poor and although he was digitalized and received theocin and salyrgan, he continued to grow worse. Two days prior to death his temperature became elevated to 100.2° F., where it remained until death, on Dec. 8, 1936.

Autopsy.—The autopsy (No. 16964) was done six and a half hours after death by one of us (W. L. A.).

External examination revealed a well-developed, poorly nourished white man about 60 years of age. The neck vessels were distended, and there was moderate edema of the lower extremities and scrotum.

The skull and central nervous system were grossly normal.

The pericardium appeared to be normal. The heart weighed 750 gm., and the cardiac enlargement was generalized. The apex extended outward to the fifth intercostal space in the anterior axillary line. The epicardial surface was smooth except for a white "soldier" spot on the anterior ventricular wall. The right auricle was moderately distended with clotted blood and the auricular appendage contained several small thrombi. The tricuspid ring was dilated, but the leaflets were normal. The right ventricle was moderately dilated and the wall hypertrophied, measuring from 4 to 8 mm. in thickness. The left auricle was dilated, and the auricular appendage was clear. The mitral ring was moderately dilated, measuring 13 cm. in circumference. Both leaflets were slightly thickened, and there was a ragged perforation, measuring 6 mm. in diameter, of the posterior leaflet. The left ventricular chamber was moderately dilated and the wall hypertrophied, measuring 2 cm. in average thickness. The aortic valve was shown to be incompetent by the water test, and when opened was found to measure 10 cm. in circumference. There were mild thickening, slight calcification, and rolling of the edges of all cusps, with retraction downward and spreading of the commissures, which measured 6-10 mm. in width. The right and posterior cusps showed identical perforations through their walls, measuring 5 mm. in diameter. There were small friable vegetations around the edges of these perforations.

Just proximal to the posterior commissure there was a mycotic aneurysm in the membranous septum measuring 8 mm. in diameter and filled with ante-mortem thrombus. Small friable vegetations surrounded the edges of this sac. Another saccular aneurysm 1 cm. in diameter was found just proximal to the left commissure, and extended 1 cm. into the folds of the membranous septum. This was also filled with thrombus, and friable vegetations were present on the edge of this sac.

Aside from some narrowing of the orifice of the right coronary artery, the vessels appeared normal throughout. The aorta was moderately dilated (9 to 11 cm.)

and showed numerous small atheromatous areas as well as pearly gray plaques and longitudinal "tree-bark" wrinklings of the intima which extended into the abdominal aorta. Approximately 2 cm. distal to the orifice of the superior mesenteric artery there was a thrombus, apparently of embolic origin, plugging the lumen. This plug extended for a distance of 1.5 cm. and did not appear to be attached to the wall of the vessel.

Bilateral pleural effusion (800 to 1000 c.c.) was present. In the right lung near the periphery there were two triangular infarcts with ante-mortem clots demonstrable in the vessels supplying these areas. The lungs were otherwise normal. All loops

Fig. 1.—Case 1, Autopsy No. 16964. Photograph of heart. Extensive aortitis with widening of the commissures of the aortic cusps is evident. Straws have been placed through perforations in the cusps and one through a perforation in the mitral leaflet. Between the two aortic cusps bordering the muscle may be seen a mycotic aneurysm surrounded by small vegetations.

of the small intestine, also the cecum and the first portion of the ascending colon, were distended. The serosa was reddish-purple in color. The serosal surfaces were covered with thin, fibrinous exudate, and a small amount of serosanguineous fluid was found in the peritoneal cavity in the pelvis. The liver was slightly enlarged and presented a typical "nutmeg" appearance on gross section. The gall bladder and biliary ducts were normal. The spleen showed a well-marked chronic passive congestion.

Both kidneys revealed marked passive congestion. The ureters and bladder were normal, except for some longitudinal scarring near the trigone at the base of the bladder. The prostate, which was one and a half times normal size, contained a small adenoma. In the periprostatic vessels there were numerous ante-mortem clots.

Microscopic Examination.—Aorta: The intima showed irregular fibrous thickening which in places was quite marked. There was definite calcification in one or two areas. The media contained many small and some fairly large scars surrounded by moderate numbers of round cells. The adventitia showed fibrous thickening, and the vasa vasorum were thickened by an endarteritis which was quite marked in some places. One fairly large arteriole was obliterated by an organized thrombus. Round cells were rather abundant in the perivascular tissues.

Bacteriology.—Smears and cultures from the abdominal cavity, the aortic valve, and spleen, and fluid from the seminal vesicles and prostate revealed the presence of *Streptococcus viridans.*

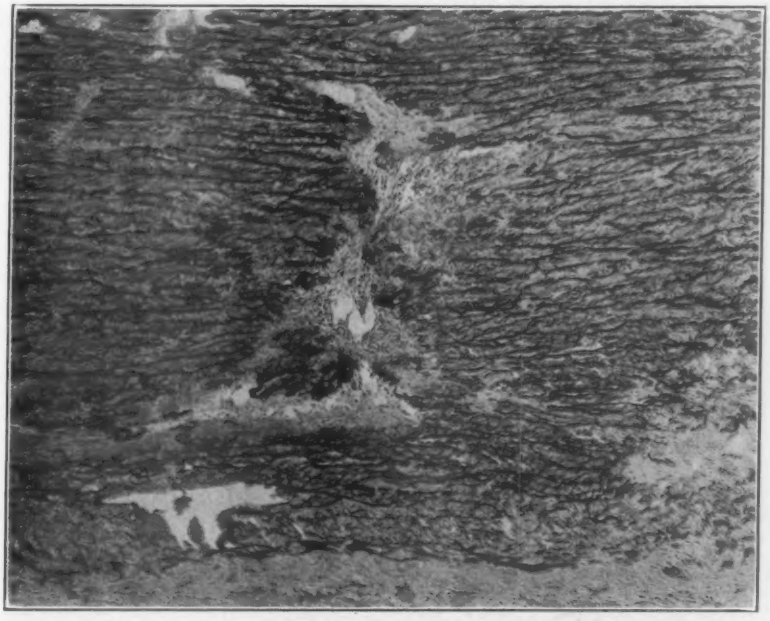

Fig. 2.—Case 1, Autopsy No. 16964. Photomicrograph of aorta showing medial scarring with destruction of elastic fibers (Elastica stain ×95).

Anatomical Diagnosis.—Syphilis of the aorta and aortic valve with insufficiency and cardiac hypertrophy; subacute bacterial endocarditis, aortic and mitral (*Streptococcus viridans*); mycotic, saccular aneurysm, membranous septum and aortic cusps, multiple; mural thrombosis of right auricular appendage; embolism of pulmonary arteries, with multiple infarction of lung; embolism of superior mesenteric artery, with infarction of small intestine, cecum, and ascending colon; acute generalized peritonitis (*Streptococcus viridans*); thrombosis of periprostatic veins; mild hypertrophy of prostate; subacute cystitis; generalized arteriosclerosis; fibrosis of bladder at trigone; operation, transurethral resection, healed.

Discussion.—The diagnosis of syphilis in this case was well established both by the history and the laboratory and pathologic findings. Clinically, the aortitis and aortic insufficiency were quite evident. How-

ever, the presence of bacterial endocarditis was not suspected, and probably justifiably so, inasmuch as there was no fever. Also, the absence of early embolic phenomena was a contributing factor in the failure to make a clinical diagnosis of bacterial endocarditis. The disturbances in the mechanism of the heart beat which occurred two weeks prior to death (change from sinus rhythm to flutter and reversion to normal rhythm upon digitalization) were probably due to the destructive lesion found in the membranous septum at autopsy. Judging from the unusual degree of ulceration with invasion deep into the septum by the bacterial process, one must assume that the lesion was present for a longer time than the clinical manifestations would suggest. One cannot account for the absence of earlier and more abundant embolic phenomena.

CASE 2.—Los Angeles County General Hospital, P. F. No. 474-179, Autopsy No. 14790.

C. W., a 50-year-old male negro, entered the hospital Dec. 29, 1935, in a comatose state. A brief, inadequate history from relatives stated only that he had complained of abdominal cramps about twelve hours before admission. These recurred several hours later and were associated with back pains. Shortly after the recurrence of back pain, the patient fell and lost consciousness.

Physical examination showed that the patient was in a deep stupor. The temperature was 101.8° F. (rectal); the pulse rate, 84; the respiratory rate, 42; and the blood pressure, 52/0. The pupils reacted sluggishly to light, and the eyes were deviated to the right. Moist râles were heard at the bases of the lungs. The heart tones were distant and were obscured by the breath sounds. The abdomen was not remarkable. All the deep reflexes were absent. No pathologic reflexes were obtained. There was flaccid paralysis of the entire left side. The patient expired twelve hours after admission.

Autopsy.—Autopsy No. 14790 was performed eight hours after death by Dr. J. L. Mason, and the following findings were reported. External examination showed a well-developed and well-nourished negro. There were a few petechiae in the conjunctivae. The brain appeared normal externally, but a single coronal section through the mammillary bodies revealed an area of red softening in the thalamus extending out to the cortex. The heart weighed 290 gm. Its chambers, septa, and valves were normal. Immediately distal to the aortic valve in the base of the aorta were seen numerous small, friable vegetations which were easily scraped off. The aorta was not athermatous to any marked degree and did not have the characteristic appearance of syphilitic aortitis, although it showed peculiar longitudinal corrugations of the intima.

The lungs showed only moderate congestion. The peritoneal cavity was dry. The small and large bowel were distended with serosanguineous fluid. Numerous areas of purple discoloration were seen, but no thrombi were found in the superior mesenteric artery or its branches. Recent infarcts were present in both kidneys. The skeletal, endocrine and genital systems were normal.

Microscopic Examination.—Vegetation on Aorta: Microscopic sections of the vegetation revealed an organizing fibrinous mass in which cocci were demonstrated by means of the Gram-Weigert stain.

Aorta: There was marked irregular fibrous thickening of the intima with areas of necrosis in the deeper parts, and patches of heavy cellular infiltration (in the proximity of the aortic vegetation). The media was greatly disrupted by large scars which were heavily infiltrated with round cells. The adventitia was thickened

and showed extremely heavy round-cell infiltration which was not limited to the vessels. Endarteritis was severe in the small arterioles, almost closing a number of them.

Laboratory Findings.—No post-mortem blood culture was taken. The post-mortem blood Wassermann reaction was strongly positive. The post-mortem culture of the vegetations on the aorta showed *Streptococcus viridans.* The culture from the spleen showed no growth.

Anatomical Diagnosis.—Syphilis of aorta; mycotic aortitis at root of aorta; embolism of cerebral arteries, with cerebral softening on right side; bilateral embolism of renal arteries, with multiple infarction of kidneys; embolism of mesenteric arteries, with infarction of small and large bowel.

Discussion.—Because of the fact that the patient was comatose on entry and was in the hospital less than twenty-four hours before death,

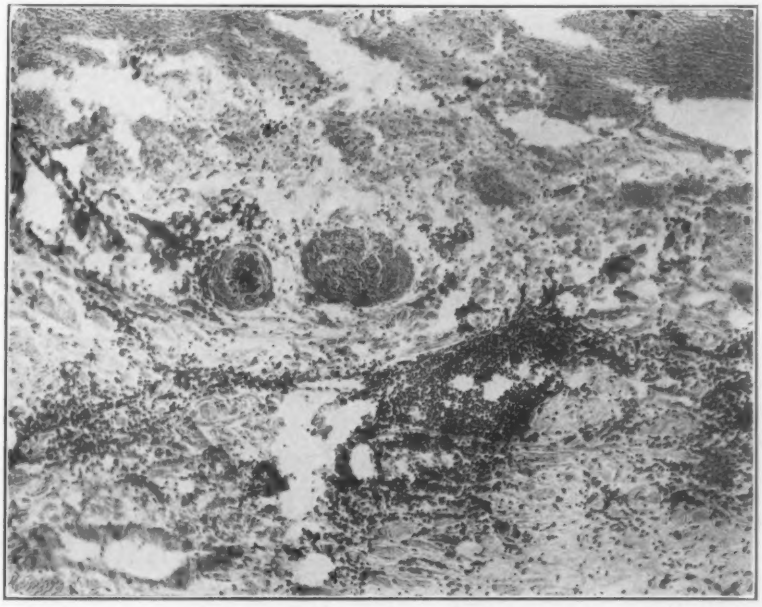

Fig. 3.—Case 2, Autopsy No. 14790. Photomicrograph of aorta showing endarteritis of the vasa vasorum, fibrous thickening of adventitia, and heavy round-cell infiltration (hematoxylin and eosin stain ×95).

the history was incomplete. Autopsy disclosed the presence of syphilitic aortitis. That there was a superimposed bacterial aortitis was evident from the septic emboli which were found in the brain, kidneys and intestines, as well as from the fact that the *Streptococcus viridans* grew in the post-mortem culture from the aortic vegetations.

CASE 3.—Los Angeles County General Hospital, P. F. No. 343-434, Autopsy No. 16170.

R. F., a 43-year-old Mexican housewife, entered the hospital April 24, 1936, because of vaginal bleeding, associated with a mucopurulent vaginal discharge of four days' duration, and lower abdominal pain of one month's duration. Prior to this the patient had had no vaginal bleeding for five years. Physical examination at this time revealed a well-developed, middle-aged Mexican woman. The oral tempera-

ture was 100.8° F.; the pulse rate, 120; the respiratory rate, 20; and the blood pressure, 135/70. Positive findings included questionable enlargement of the fundus of the uterus, which appeared fixed and somewhat soft; thickening of both broad ligaments; tenderness in the left lower quadrant; a purpuric eruption of the skin of the legs and feet; pupils which reacted poorly to light, but reacted well in accommodation; and a systolic murmur over the apex of the heart.

While she was in the hospital, her temperature was elevated to 100-101° F. daily. The blood Wassermann reaction was found to be strongly positive. Diagnoses of pelvic inflammatory disease and syphilis were made, and the patient was discharged May 12, 1936. The patient was treated in the Venereal Disease Clinic after discharge. She received 0.1 gram of bismocymol on May 18, June 17, and June 24, 1936. On May 22, 1936, a spinal puncture was done; the cell count, the globulin content, and the pressure were normal, and the Wassermann and Kahn tests were negative. One week following the spinal puncture, she developed headache and vomiting which persisted for two weeks.

She was readmitted to the hospital July 13, 1936. Physical examination revealed that the oral temperature was 100° F.; the pulse rate, 102; the respiratory rate, 22; and the blood pressure, 128/72. The patient was conscious and rational. There was moderate rigidity of the neck. There was a generalized lymphadenopathy. A bismuth line was noted on the gums. There was a petechial eruption over the abdomen. A systolic murmur was noted at the apex.

A spinal puncture was again performed. The initial pressure was 270 mm. of water. The fluid was cloudy; it contained 2000 cells per cubic millimeter, mainly polymorphonuclear leucocytes. No organisms grew in the culture. The spinal fluid sugar was 87 mg. per 100 c.c.

The treatment consisted of repeated spinal punctures. *Streptococcus viridans* was found on one culture. The spinal fluid Wassermann was repeatedly negative. A blood Wassermann on July 15, 1936, was negative. One blood culture showed a large gram-positive rod which was considered a contaminant. The meningeal signs cleared, and the patient appeared remarkably improved. However, she suddenly became cyanotic and dyspneic and died very abruptly on July 21, 1936.

Autopsy No. 16170 was performed by one of us (H. E. M.) eighteen hours after death.

Numerous small petechiae were seen over the trunk and extremities.

The brain showed marked pial congestion with a very small amount of milky, nonpurulent fluid in the sulci over the vertex. Numerous coronal sections of the brain revealed no abnormalities.

Petechiae were seen in the visceral pericardium. There were firm, fibrous, pericardial adhesions between the aorta and pulmonary artery at the base of the heart. Section was made through this area and thick, yellow-green pus was found just beneath the pericardium in the small triangular space between the origin of the aorta and the pulmonary artery. This abscess communicated directly with a vegetation on the aorta, which had perforated the wall. The heart weighed 530 gm. The chambers on the right side of the heart appeared moderately dilated. The left ventricle also showed dilatation. Its wall averaged 1 cm. in thickness. The tricuspid, pulmonic, and mitral valves were normal. Several small, pale yellow plaques were seen in the free margins of the cusps of the aortic valve. The commissures showed slight widening. The base and attachment of the aortic valve appeared to be calcified. About 1 cm. above the aortic ring there were several ulcerated plaques in the intima of the aorta. On one of these there was a grayish yellow vegetation which measured approximately 5 mm. in diameter. This vegetation had eroded through the wall of the aorta and communicated directly with the small abscess cavity previously described. The aorta showed some longitudinal wrinkling of the

intima and occasional white, elevated plaques in the thoracic portion. Elsewhere, the intima was smooth. The coronary arteries and myocardium appeared normal.

The lungs showed marked edema and bilateral, healed, apical tuberculosis. The spleen weighed 275 gm. and showed moderate softening. A fibromyoma of the uterus was found, as well as a submucous, endometrial polyp. Both tubes and ovaries were prolapsed into the cul-de-sac, where they were adherent to each other and to the adjacent structures. The tubes were moderately dilated. The ovaries appeared normal on cross section. The kidneys showed a peculiar mottled reddish yellow appearance.

Microscopic Examination.—In the aorta in the region of the vegetation there were deposits of fibrin in which were entangled large collections of disintegrated polymorphonuclear cells, red blood cells, and occasional fibroblasts, replacing large areas of the intima, which appeared ulcerated. The media showed areas of necrosis and

Fig. 4.—Case 3, Autopsy No. 16170. Photomicrograph of aorta. Scarring is evident about the vasa vasorum of the media with more or less round-cell infiltration (hematoxylin and eosin ×95).

ulceration similar to those in the intima and continuous with them. In several areas in the media there were large collections of round cells, mainly perivascular in distribution.

Elsewhere in the aorta the intima was only moderately thickened by loosely arranged cellular connective tissue. The media contained a moderate number of small scars surrounded by quite heavy round-cell infiltration. Other areas showed marked destruction of the media by large, almost confluent scars. A good many polymorphonuclear leucocytes were found in these areas. Endarteritis of the adventitial arterioles was marked, with eccentric thickening of the walls. Dense accumulations of round cells were found about the vessels and well into the adjacent adipose tissue. Fibroblasts were present in several areas.

Laboratory Findings.—A hemolytic streptococcus was recovered from the blood post mortem.

Anatomical Diagnosis.—Syphilis of aorta and aortic valve, with cardiac hypertrophy; septic thrombosis of aorta, with perforation and abscess formation involving base of heart; septicemia (*Streptococcus hemolyticus*); acute septic splenitis; purulent meningitis, healed; fibromyomas of uterus; polyp of uterus; subacute cystitis; acute, bilateral pyelitis; bilateral apical, healed, pulmonary tuberculosis; chronic bilateral oophoritis and salpingitis.

Discussion.—The diagnosis of syphilis was established clinically in this case, although no history was obtained as to the time of infection. The septicemia and the vegetative aortitis were not discovered until autopsy, although the patient presented purpuric phenomena and had fever and irregular menstrual bleeding several months before death. It is of interest that the embolic meningitis had practically cleared up before death. At autopsy there was no evidence of syphilis of the central nervous system. The principal syphilitic lesion of the cardiovascular system was in the aorta, although early changes were present in the aortic valve. It is of interest that the vegetation in the aorta had perforated the wall of the vessel in the one location where a perforation could be readily walled off, i.e., near the base of the heart. Although one spinal fluid culture, ante mortem, was reported as containing *Streptococcus viridans*, all of the post-mortem cultures showed *Streptococcus hemolyticus*.

CASE 4.—Los Angeles County General Hospital, P. F. No. 283-667, Autopsy No. 16645.

L. T. F., a 28-year-old white male chemist, came to the hospital April 5, 1935, because of abdominal pain and vomiting. One year before an appendectomy had been done. Physical examination gave essentially negative results, except that the aortic second sound was replaced by a to-and-fro murmur. The blood Wassermann and Kahn reactions were strongly positive. The abdominal pain disappeared, and the patient was referred to the Venereal Disease Clinic for treatment.

He was readmitted in May, 1936. Additional history at this time revealed that he had suffered from dyspnea and precordial pain on exertion since 1934. There was no history of a chancre. He had had acute urethritis in 1927, which had been followed by polyarthritis for six months. Examination revealed a to-and-fro murmur in the aortic area and a diastolic murmur and thrill at the apex. Capillary pulsations and Duroziez' sign were present. The blood pressure was 170/30.

The final admission was on Oct. 3, 1936. The patient returned to the hospital because of increased weakness, loss of weight, and severe night sweats. The cardiac findings were the same as in May, 1936. There was daily elevation of the temperature to 100° F., and the pulse rate was 100 to 120 per minute. Petechiae were seen in the conjunctivae. The spleen was easily palpable at the costal border.

Laboratory Examination.—The hemoglobin was 70 per cent (Sahli); the erythrocyte count, 3,900,000; and the leucocyte count, 8,000. The urine contained no albumin, casts or cells. An orthodiagram showed marked cardiac enlargement, predominantly left ventricular. The electrocardiogram revealed signs of myocardial impairment and left axis deviation. *Streptococcus viridans* was found in three separate blood cultures.

Autopsy No. 16645 was performed by one of us (H. E. M.) three and one-half hours after death.

Fig. 5.

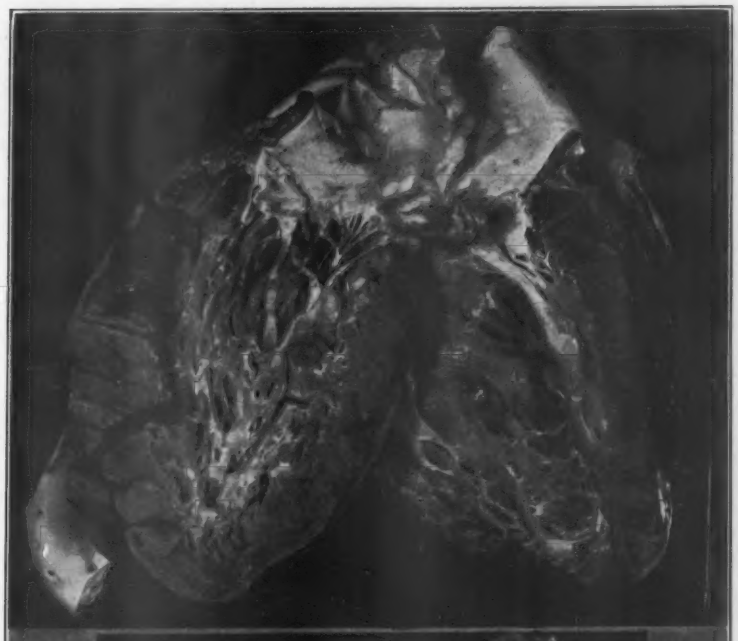

Fig. 6.

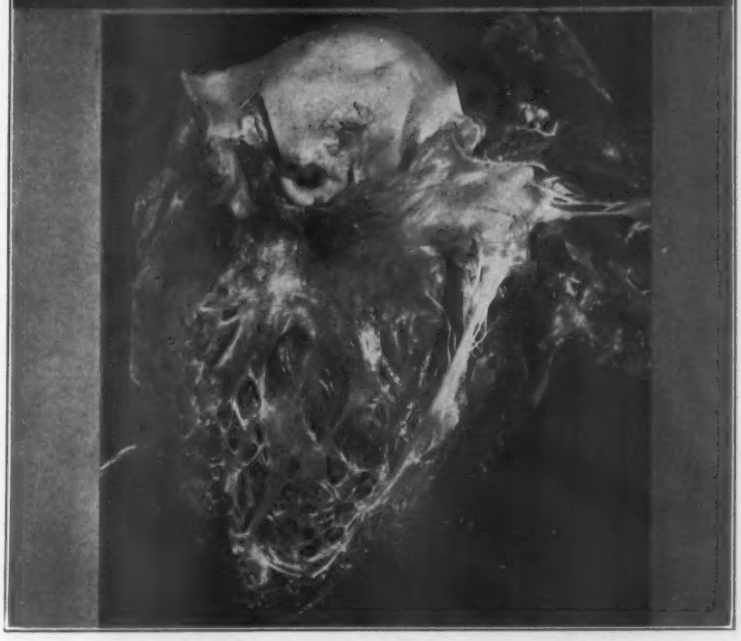

Fig. 5.—Case 4, Autopsy No. 16645. Photograph of the heart. The mitral valve shows fibrous thickening and fusion of the leaflets, thickening and shortening of the chordae tendineae, evidently an old rheumatic lesion. A bacterial vegetation covers the posterior leaflet. The wall of the auricle is definitely thickened.

Fig. 6.—Case 4, Autopsy No. 16645. Photograph of the heart. This shows widening of the commissures of the aortic valve with shortening and rolling of the cusps. A peculiar, depressed, scarlike plaque is present immediately above the middle commissure. A block for section has been removed from a similar lesion to the left of the right coronary ostium. Elsewhere the base of the aorta is very smooth.

There was marked thickening of the pia-arachnoid, with areas of fibrosis over the vertex of the brain. Small petechiae were scattered throughout the white substance of the brain.

There were many fibrous plaques in the visceral pericardium over the anterior surface of the heart, as well as diffuse thickening of the parietal pericardium. The heart weighed 600 gm.; the cardiac hypertrophy was practically limited to the left ventricle and left auricle. The right auricle was moderately dilated. The right ventricle appeared approximately normal in size. The wall of the left auricle was between two and three times thicker than normal and showed areas of scarring in its endocardium. Both auricular appendages appeared normal. The tricuspid valve showed slight thickening of the leaflets, but was not otherwise remarkable. It measured 11.5 cm. in circumference. The pulmonic valve was normal and measured 8 cm. in circumference. The mitral valve showed fibrous thickening of the leaflets, with one area of calcification along the line of attachment at the base of the valve.

Fig. 7.—Case 4, Autopsy No. 16645.—Photomicrograph taken through the plaque in the base of the aorta (see Fig. 6). There are marked fibrous thickening and heavy round-cell infiltration of the adventitia. The outer part of the media is also involved.

There were some thickening and shortening of the chordae tendineae. There was a large, yellow, granular, heaped-up vegetation on the mitral valve, approximately 2 cm. in diameter. In addition, there were numerous pinpoint vegetations along the line of closure. The mitral ring measured 9.5 cm. in circumference. The aortic valve was markedly distorted and displaced downward. Its circumference was 7.2 cm. The commissures appeared widened and there was rolling of the free margins of the cusps. There were ulceration and scarring of the cusps by large, granular vegetations similar to those on the mitral valve. Just above the aortic ring in the aorta were two pearly white plaques. These plaques extended down to the commissures and appeared to widen them. The pulmonary artery and the coronary arteries were essentially normal. Repeated broad sections of the myocardium revealed a dark red heart muscle in which were scattered many small and large areas of fibrosis.

Recent infarcts were seen in the spleen and kidneys. Bronchopneumonia was present. No other positive findings were recorded.

Microscopic Examination.—Heart: Several sections revealed large areas of dense scarring. Elsewhere many smaller scars were present, some in the form of narrow bands of fibrous tissue. The muscle fibers were hypertrophied and irregularly arranged. Occasional areas of recent necrosis were seen. Many large mononuclear cells of elongated form, together with occasional lymphocytes and polymorphonuclear leucocytes, diffusely infiltrated the interstitial tissue. Several typical Aschoff bodies were seen in sections of the interventricular septum.

Aorta, Through Plaque: The intima was markedly thickened by dense fibrous tissue which contained some pale atheromatous areas. The media in this region was much thinned and scarred. Heavy deposits of round cells were found about the scars and extending into the adjacent portions of the adventitia. The latter was markedly thickened and densely fibrous in this area. Small perivascular collections of round cells were scattered throughout. A moderate amount of endarteritis was present.

Laboratory Findings.—*Streptococcus viridans* was recovered from the vegetation on the heart valve.

Anatomical Diagnosis.—Syphilis of aorta, focal; syphilis of aortic valve with insufficiency and cardiac hypertrophy; chronic rheumatic endocarditis, mitral valve; subacute bacterial endocarditis, mitral and aortic valves (*Streptococcus viridans*); embolism of splenic artery, with infarction of spleen; embolism of renal artery, with infarction of kidneys, and terminal bronchopneumonia.

Discussion.—On the last two admissions it was thought that the heart disease was rheumatic in origin, with involvement of the aortic and mitral valves and superimposed bacterial endocarditis. Pathologically, the heart valves were thought to be the seat of a double lesion, viz., syphilitic valvulitis of the aortic valve, and rheumatic endocarditis of the mitral valve.

Syphilitic involvement of the aorta by two focal lesions with the remainder of the intima normal in appearance is extremely rare. It may be questioned whether such lesions are of syphilitic origin. The changes in the aortic valve, however, in no way resembled rheumatic endocarditis. The commissures in the vicinity of the aortic plaques were definitely widened, and the free edges of the cusps were rolled and somewhat shortened. The microscopic picture was that of syphilis, as described above. The infiltrating cells were of the lymphocytic and plasma cell varieties rather than of the large mononuclear type seen in rheumatic lesions. In addition, the positive serologic reactions strengthen the evidence that the lesions were syphilitic.

CASE 5.—Los Angeles County General Hospital, P. F. No. 457-597, Autopsy No. 14326.

T. P. J., a negro, aged 42 years, a bootblack, was addittted to the hospital Sept. 25, 1935. He was in excellent health until Sept. 9, 1935, when, upon returning from work, he had a chill followed by a fever of 103° F. Following this he had a severe headache, became extremely weak, and upon trying to get out of bed fainted and fell to the floor. He remained in bed at home until the morning of admission, when he again had a fainting spell. Aside from slight palpitation and dyspnea on exertion, he had been without symptoms until the onset of the present illness.

The past history was irrelevant except for the fact that he had had a chancre at the age of 16, following which he received sixteen "intravenous injections."

Physical examination showed that the patient was fairly well developed. The temperature was 101.3° F.; the pulse rate, 80; the respiratory rate, 34; and the blood pressure, 134/0. The right pupil was irregular, but both pupils reacted well to light and in accommodation. There were "explosive" carotid pulsations in the neck. The fingers showed definite clubbing, and the pulse was of the Corrigan type. The lungs were normal except for crackling râles at the left base. There was a heaving precordium with the point of maximum intensity centered in the fifth interspace just to the left of the nipple. There was a palpable diastolic thrill at the apex. There was also a soft, low-pitched systolic murmur in the aortic area. There was a loud, blowing, to-and-fro murmur at the apex which was transmitted upward toward the base. The rhythm was normal. The abdomen was essentially negative. There was no dependent edema. The reflexes were normal.

Laboratory Examination.—The blood Wassermann and Kahn reactions were strongly positive. The hemoglobin was 65 per cent (Sahli); the erythrocyte count, 2,750,000; and the leucocyte count, 26,000; the differential leucocyte count showed that 88 per cent were polymorphonuclears, 8 per cent lymphocytes, 3 per cent monocytes, and 1 per cent basophils. The urine was normal. Blood cultures made Oct. 4 and 8, 1935, remained sterile.

A roentgenogram of the chest, made Oct. 1, 1935, led to a diagnosis of aortic heart disease. Agglutination tests for typhoid and undulant fever, done Oct. 12, 1935, were negative.

Course.—The patient continued to run a fever of 101 to 103° F., and on Oct. 4, 1935, a friction rub was heard at the apex of the heart. He grew progressively worse, and expired October 12.

Autopsy No. 14326 was done by Dr. J. P. FitzGibbon twelve hours after death. The body was that of a well-developed, middle-aged negro male, showing no gross abnormalities.

The pericardial sac was tremendously enlarged, and when it was opened it seemed to enclose snugly the large heart; the visceral pericardium was tremendously roughened by a heavy, shaggy, fibrinous exudate, which was firm and more or less organized. This process was less marked on the parietal pericardium. The heart weighed 750 gm. The right auricle and ventricle were approximately of normal size. The left auricle was slightly enlarged and the left ventricle was greatly enlarged and thickened, the wall averaging 1.9 cm. in thickness. The endocardial surface of the left ventricle showed marked tigering. The valves were normal, except for the aortic valve, whose edges were rolled and whose mitral cusp was the seat of an acute process which had progressed to the formation of a mycotic aneurysm with rupture at one point. One centimeter below the aortic orifice, in the region of the septum, there was a square patch about 1 cm. across which was slightly raised, firm, and, when cut, appeared as a yellow-gray, necrotic plaque. The aorta was the seat of a number of "tree-bark" wrinklings and, in addition, showed many areas of arteriosclerotic involvement. Each pleural cavity contained 500 c.c. of thin, straw-colored fluid.

Unfortunately no microscopic examination of the aorta was made in this case, and there is no material available for study.

Laboratory Findings.—*Streptococcus viridans* and *E. coli* were recovered from the vegetation. A culture from the pericardium became contaminated.

Anatomical Diagnosis.—Syphilis of aorta and aortic valve with insufficiency and cardiac hypertrophy; acute bacterial endocarditis; subacute fibrinous pericarditis; and splenic tumor, septic.

Discussion.—This is a fairly typical case of combined bacterial endocarditis and syphilitic valvulitis, both from the clinical and gross patho-

logic standpoints. The febrile course was septic from the onset of the final illness. It is unfortunate that more attempts were not made to obtain a positive blood culture prior to death.

SUMMARY

Five cases of proved syphilitic endocarditis or aortitis, with superimposed bacterial vegetations, have been presented. In none of the cases were both diagnoses made clinically. In all five cases the blood Wassermann and Kahn reactions were positive. In four cases blood cultures were positive, and in the fifth case *Streptococcus viridans* was grown from the vegetation on the heart valve.

Streptococcus viridans was recovered in four of the cases and *Streptococcus hemolyticus* in the remaining case. In three of the cases embolic phenomena were prominent, and in two the mesenteric vessels were involved. In one case there were multiple saccular mycotic aneurysms of the membranous septum and aortic cusps. In another case a fairly characteristic syphilitic aortic valvulitis and aortitis were associated with a typical rheumatic involvement of the mitral valve.

The diagnosis of syphilitic aortitis and valvulitis does not exclude the possibility of superimposed bacterial involvement, as shown by the above cases, although the lesion undoubtedly is rare. This diagnosis should be considered clinically whenever there is a combination of sepsis of undetermined origin, a positive Wassermann reaction, and evidence of aortic insufficiency or aortitis, without evidence of previous rheumatic infection.

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COMPLETE TRANSPOSITION OF THE GREAT VESSELS

Clinical and Pathologic Features*

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COMPLETE transposition of the great vessels is such a striking malformation of the heart that it has attracted the attention of a number of investigators. During recent years most of the studies[1-5] have been directed toward the origin of this condition. Various theories based upon embryologic, morphologic, and phylogenetic studies have been advanced. Recently Lev and Saphir[6] reviewed these theories and reported the autopsy findings in 6 cases of complete transposition. There have also been a number of isolated case reports,[7-12] but no progress has been made in regard to the clinical recognition of this condition. In 1930 Kato[13] reviewed 92 cases which had been reported in the literature and added 5 more. He emphasized the wide variety of malformations which occur in association with transposition of the great vessels. His analyses showed that there were no characteristic murmurs or thrills associated with this malformation, and he expressed the opinion that the condition was extremely difficult, if not impossible, to recognize during life. Castellanos and his coworkers[14] have recently made an extensive report concerning the recognition of congenital malformations of the heart by visualizing the chambers of the heart with a radiopaque substance, thorotrast. They claimed that transposition of the great vessels could be recognized by this method because the solution which was injected into the jugular vein passed directly from the right side of the heart into the descending aorta. The method requires special radiologic technique and also involves the risk of possible untoward reactions. Furthermore, the method does not permit differentiation of complete transposition of the great vessels from other malformations in which the blood from the pulmonary circulation is pumped directly into the aorta. Recently, Ingham and Willius[15] have reported five cases; they concluded that there were no characteristic physical signs or symptoms. During the last few years we have had the opportunity to make clinical studies on four cases. The fluoroscopic findings in these cases were sufficiently characteristic to enable the diagnosis to be made during life.

The fundamental feature in cases of complete transposition of the great vessels is the abnormal torsion of the aortic septum, whereby the aorta arises from the right ventricle and the pulmonary artery

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from the left ventricle. Thus the blood is pumped from the right ventricle through the aorta to the systemic circulation and returns via the superior and inferior venae cavae to the right auricle; the blood from the left ventricle is pumped through the pulmonary artery to the lungs and returns by way of the pulmonary veins to the left auricle. Obviously, in order that this malformation may be compatible with life, even for a short time, there must be an additional malformation which permits some crossing of the systemic and pulmonic circulations, i.e., either a patent ductus arteriosus, a patent foramen ovale, an interventricular septal defect, or some combination of these.

It is the large number of variations in the associated anomalies which renders the condition difficult to diagnose during life. These different concomitant malformations produce various changes. Although the quality and intensity of the murmurs and thrills vary according to the nature of the concomitant malformation, they depend primarily upon the relative pressure in the systemic and pulmonic circulations. These several factors permit such wide diversity of physical findings that the murmurs and thrills are of no diagnostic aid. Furthermore, the different combinations of anomalies cause a variety of changes in the size and shape of the heart. This makes the exact diagnosis of the malformation difficult. The problem resolves itself into (1) the recognition of the transposition and (2) an analysis of the concomitant malformations. The purpose of this report is to present the features by which the existence of complete transposition of the great vessels can be recognized during life.

The diagnosis is based primarily upon the changes in the shadow cast by the great vessels, combined with persistent cyanosis. Inasmuch as the right ventricle pumps the unoxygenated blood through the systemic circulation, sooner or later the patient always shows *persistent cyanosis*. Both the time at which the cyanosis becomes apparent and its intensity vary with the concomitant malformation. Although we have seen one infant in whom no cyanosis was visible in the neonatal period, as yet we have not recognized the condition before cyanosis appeared.

The altered position of the great vessels relative to the ventricles causes such a characteristic change in the cardiac silhouette that the condition can be recognized by fluoroscopic examination. The most significant feature is the alteration of the shadow cast by the great vessels. When the aorta arises from the right ventricle and the pulmonary artery from the left ventricle, the aorta lies anteriorly and further to the left than it does in the normal heart, and the pulmonary artery lies posteriorly and further to the right (Fig. 1). Because of this counterclockwise rotation the pulmonary artery comes to lie behind the aorta and the shadow cast by the great vessels is narrow. Upon rotating the infant into the left anterior oblique position, the

pulmonary artery, which in the anteroposterior view was behind the aorta, comes to lie parallel to the aorta and thereby causes the shadow cast by these vessels to increase in width (Fig. 2). By placing one finger behind the other and then rotating the hand 45°, the change in the width of the shadow can be clearly demonstrated. Because of the difficulties in obtaining satisfactory roentgenograms in infancy,* especially in the oblique position, this phenomenon may be difficult to demonstrate. These changes are, however, readily visualized beneath the fluoroscope. They are pathognomonic of the condition.

The shape of the heart is also suggestive. In the anteroposterior view, in addition to the narrow aortic shadow, the heart is seen to be

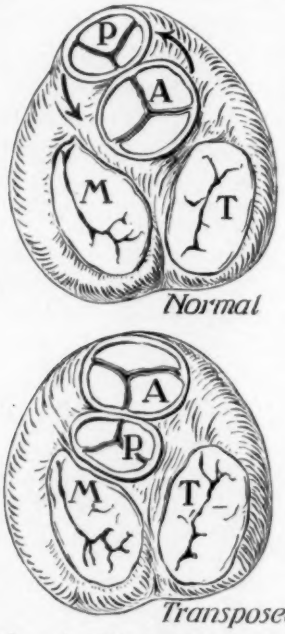

Fig. 1.—The upper diagram shows the base of the heart with auricles removed and the direction of the rotation of the great vessels. (From W. Spalteholtz—*Handatlas der Anatomie.*)

The lower drawing shows the position of the pulmonary artery and aorta in cases of transposition of the great vessels.

enlarged both to the right and the left (Fig. 3). Not only is the heart enlarged, but, inasmuch as the right ventricle pumps the blood through the systemic circulation, there is always specific enlargement of that chamber. This is best recognized under the fluoroscope in the left anterior oblique position; in this view the right ventricle is seen to project forward anterior to the aorta.

*We have had great difficulty in obtaining satisfactory roentgenograms in cases of transposition of the great vessels. Characteristic teleoroentgenograms are shown by Kato,[13] Feldman and Chalmers,[9] and in Abbott's *Atlas of Congenital Heart Disease*[16] (Dr. Nicolson's case, page 54).

The absence of the shadow cast by the pulmonary conus of the right ventricle offers additional evidence that the pulmonary artery occupies an abnormal position. The absence of the pulmonary conus of the right ventricle is due to the fact that the aorta seldom lies as far to the right as does the normal pulmonary artery. Thus, in the anteroposterior view it is usual to find that the shadow ordinarily cast by the pulmonary conus of the right ventricle is absent; this causes a

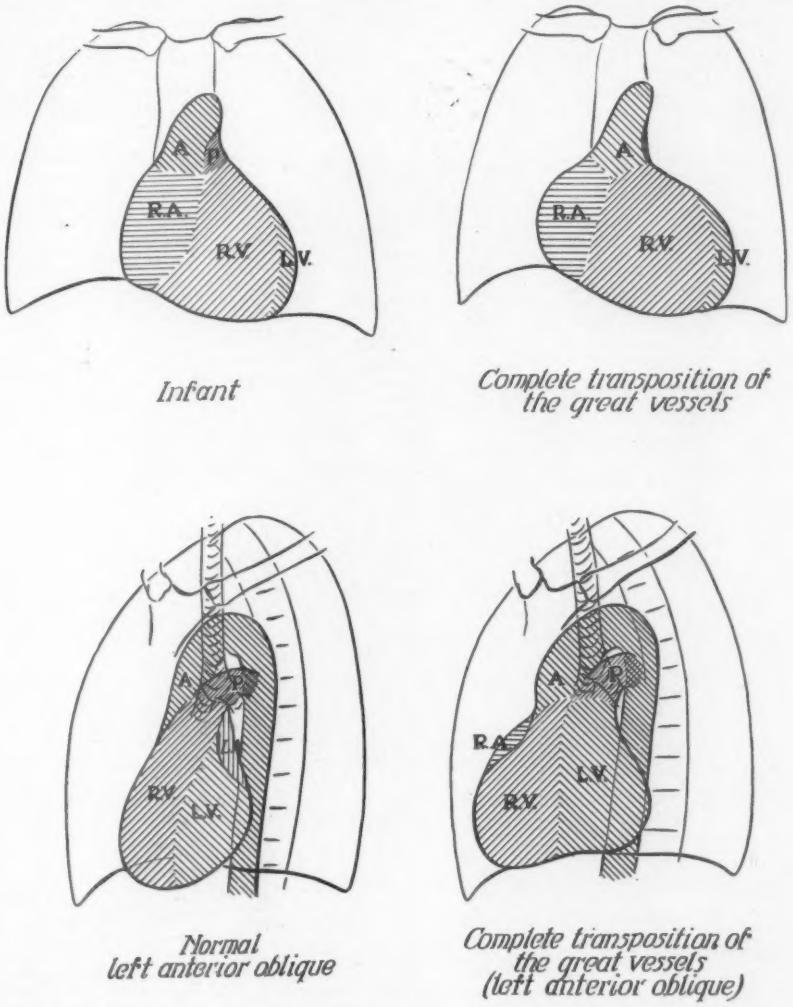

Fig. 2.—The upper diagrams illustrate the anteroposterior view of the heart of the normal infant and when transposition of the great vessels is present.

Note: The great vessels appear narrower in the transposed heart than in the normal heart.

The lower diagrams illustrate the changes which occur in the left anterior oblique position.

Note: In this view the great vessels appear wider than in the normal heart; thus, upon rotation there is a greater change in the width of the great vessels in cases of transposition than occurs in the normal heart. In this position the right auricle may or may not be visible.

slight concavity, rather than a convexity, of the upper border of the cardiac silhouette to the left of the sternum. This abnormality may be so marked as to resemble the contour seen in cases of pulmonary atresia and nonfunctioning right ventricle.[17] Nevertheless, when the infant is rotated into the left anterior oblique position, the two conditions are easily differentiated. In cases in which the right ventricle does not function it is not enlarged, whereas in cases of transposition of the great vessels, the right ventricle is always enlarged.

The electrocardiogram may be of aid in the recognition of right ventricular enlargement. A difficulty arises because in some cases the left ventricle is also enlarged and the enlargement of the right side

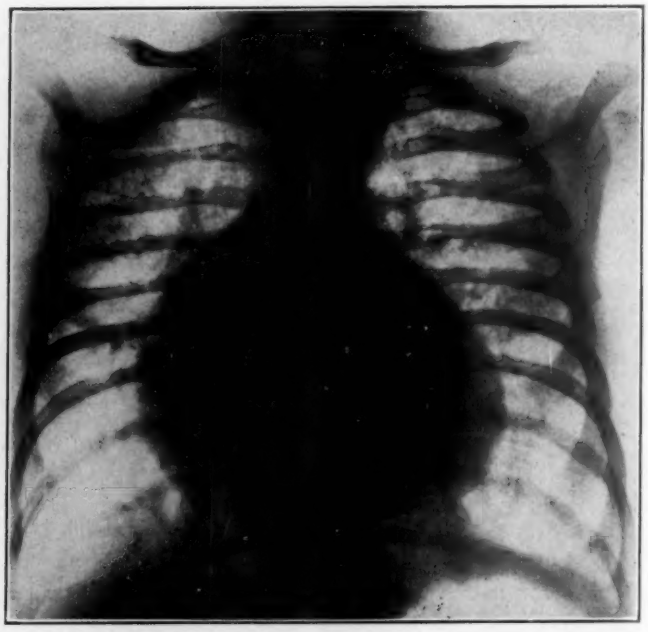

Fig. 3.—Teleoroentgenogram of the chest of an infant with complete transposition of the great vessels combined with a patent foramen ovale, patent ductus arteriosus, and a defect in the interventricular septum.

of the heart may not be sufficiently greater than the left to give right axis deviation. Therefore, the visual evidence of right ventricular enlargement is more reliable than that derived from the electrocardiogram.

As previously stated, this malformation is not compatible with life, even for a short time, unless it is associated with some additional malformation which will permit some admixture of blood between the two circulations. The various combinations of anomalies manifest themselves by slightly different features which are of aid in diagnosis, but the analysis of these manifestations is beyond the scope of the present paper, and will be reported in detail at a later date.

SUMMARY

We have had the opportunity to study four cases of complete transposition of the great vessels clinically and post mortem. In one case there was, in addition, a patent foramen ovale, a patent interventricular septum, and a patent ductus arteriosus; in the second, a patent interventricular septum; in the third, a patent foramen ovale and a patent ductus arteriosus; and in the fourth, a patent foramen ovale, a patent ductus arteriosus, and complete interruption of the isthmus of the aorta. Each had its own individual variations, but all showed the characteristic features of complete transposition of the great vessels, namely, (1) persistent cyanosis; (2) cardiac enlargement, especially of the right ventricle; (3) a narrow aortic shadow in the anteroposterior roentgenogram; and (4) an increase in the width of the roentgenographic shadow cast by the great vessels when the patient is placed in the left anterior oblique position.

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SOME NOTES ON THE ANATOMY OF THE ELEPHANT'S HEART*

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THE rare opportunity to dissect the hearts of two captive elephants is the occasion for the presentation herewith of a few notes concerning our findings.

Its immense size is the feature that has especially aroused the interest of mankind in the elephant. As early as the time of the elder Pliny there were current many stories and speculations about the elephant. Galen[1] described the four chambers which he found in an elephant's heart which was about to be served for luncheon at the emperor's table. Since that day numerous scientific observations have been recorded. These studies have contributed to our store of information in comparative anatomy, furthering our interest in, and our knowledge of, the animal kingdom. Complete and detailed anatomic studies, however, have not often been possible on account of the degenerative changes that usually occur in the tissues in the interval between the death of the animal and the performance of the autopsy. The most recent reports concerning the elephant are those of Hill[2] (1936) and Benedict[3] (1936). The former studied the heart of the wild elephant with especial reference to the coronary vessels. Benedict, of the Carnegie Institution, published a comprehensive review of the literature dealing with the elephant and the results of intensive physiologic studies made on the animal.

In a study of the pulse rate of vertebrate animals, Buchanan[4] shows in general that "the more active animals have relatively the largest hearts and correspondingly the slowest pulses." She finds that the percentage of heart weight in relation to the body weight in the hen is 0.42 per cent, in the pigeon 1.5 per cent, in the deer 1.15 per cent, and in man 0.59 per cent. Pütter,[5] in 1918, stated that the heart weight of the elephant is 0.44 per cent and that of the whale 0.508 per cent of the body weights, respectively. We were impressed by the data gathered from the literature as related to our own observations, which are recorded in Table I. Male elephants, while relatively fewer in number, both wild and in captivity, are usually larger than the females, and those from

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Africa are larger than those from India. It will be seen from Table I that all of the males are of unusually large size. Furthermore it appears that the greater the body weight the less the proportionate size of the heart. The ratio of 1.0 per cent as given by Gilchrist[6] has been thought explainable by the fact that the heart described by him was probably weighed with the chambers filled with blood.

TABLE I

COMPARATIVE WEIGHTS OF ELEPHANTS AND THE RATIO OF HEART TO BODY WEIGHT

OBSERVER	ANIMAL	SEX	BODY WEIGHT	WEIGHT OF HEART	PERCENTAGE OF HEART WEIGHT TO BODY WEIGHT
Fox[7] (1908)	Bolivar	Male	5440 Kg.	19.1 Kg.	0.35
Noback[8] (1931)	Kartoum	Male	4710 Kg.	22.7 Kg.	0.48
White and Burwell (1921)*	Mollie	Female	3710 Kg.	19.3 Kg.	0.52
King (1935)*	Tusko	Male	6491 Kg.	21.9 Kg.	0.34
Gilchrist[6] (1851)			1975 Kg.	19.1 Kg.	1.00

*These are the authors of the present report, publishing for the first time herewith the data on Mollie and Tusko. The years refer to the dates of the dissection of these two hearts.

For detailed studies in comparative anatomy of the heart, the reader is referred to Pütter's[5] interesting and comprehensive work, and to the description of the whale's heart by White and Kerr.[9]

Of recurring interest is Galen's report[1] that he found a "bone in the heart" of the elephant. Retzer,[10] in a review of the literature on the subject, found variance in reports as to the existence of an os cordis. He did not find one in the heart of a young elephant which he dissected. It was his opinion that bone formation, when it did occur, was at the site of the trigone fibrosa. We have not found a histologic description of the os cordis in the elephant which would distinguish between true osseous tissue and simple calcium deposit. An os cordis was not found in either of our specimens, nor was there a significant degree of fibrosis or any calcification in the heart or aorta; this is in distinct contrast to the regular finding of a bone in the ox heart, and its at least occasional finding in the hearts of the sheep and the deer.

CASE REPORTS

CASE 1.—Mollie, an adult female Indian elephant, died in the Franklin Park Zoo, Boston, Mass., at 8 A.M., April 22, 1921. Death was attributed to exhaustion after a twenty-four-hour struggle to arise from the left side "cast." The autopsy was performed the following day. The main portion of the carcass was cut up and disposed of by a fertilizer manufacturer. The skeleton was preserved for mounting at the Agassiz Museum. The heart (Fig. 1) was preserved in formalin and later studied by two of us (P. D. White and C. S. Burwell). The following notes were made at the time.

TABLE II

MEASUREMENTS OF HEART (MOLLIE)

Total weight (chambers empty of blood)	19.3 Kg. (42½ lb.)
Length	24.0 cm.
Breadth	38.0 cm.
Circumference	98.0 cm.
Mitral valve diameter	13.5 cm.
Aortic valve diameter	11.0 cm.
Left ventricle	
Thickness of wall (midway)	5.0 cm.
Thickness of wall (apex)	2.0 cm.
Aorta	
Outside diameter	12.5 cm.
Internal diameter	7.5 cm.
Thickness of wall	2.5 cm.
Diameter of coronary arteries (internal)	1.0 cm.

Fig. 1.—The frontal view of Mollie's heart with a normal adult human heart for comparison.

The heart muscle, valves, aorta, and coronary arteries were normal. There was no evidence of sclerotic change; there was one small milk spot on the pericardium. The sinoauricular and auriculoventricular nodes, as well as the auriculoventricular bundle, its branches, and the Purkinje network, were all visible beneath the endocardium. The sheath of the network was readily injected with India ink. The sinoauricular and auriculoventricular nodes and the auriculoventricular bundle and its branches were dissected.

Mollie's gross weight, as recorded at the Franklin Park Zoo, June 6, 1920, was said to be 8,180 pounds (3710 kg.). Her age at death was reputed to be 40 years.

CASE 2.—Tusko, a male Indian elephant, born in 1890, was brought into the United States when a relatively young animal. He was purchased from a small overland circus called M. L. Clark and Sons by Mr. Al G. Barnes, who exhibited him from the time of purchase in the early 1920's until May 24, 1931, when, on account of his tendency to rampage, he was sold, in Portland, Oregon, to another showman.[11] Later he was transported to Seattle. Here he was exhibited without license, kept heavily chained, and in unhygienic quarters, and inadequately fed. He was condemned by the City Health Authorities and placed in the Woodland Park Zoo on Oct. 8, 1932.

He had been proclaimed by Frank Buck and Lorenz Hagenbeck to be the largest Indian elephant in captivity,[11] and was renowned for his bad disposition. Measurements made at this time by the Park Authorities, and considered correct by the Superintendent of the Zoo, Dr. Gust Knudson,* were as follows:

Length, including trunk	18 ft.	11	in.	(577	cm.)
Height at shoulders	10 ft.	2	in.	(310	cm.)
Circumference of trunk		17½	in.	(44.5	cm.)
Circumference of foot at base		65	in.	(165	cm.)
Distance between eyes	2 ft.	9	in.	(84	cm.)
Total body weight said to be		14,313	lb.	(6491	kg.)

In the zoo Tusko was the most prized possession and accordingly received the best of care. Exercise was afforded by a one mile walk twice a week. The food consisted of hay, vegetables, and grain. Particular precaution was taken to avoid annoyance by visitors. He remained in the zoo throughout the fall, winter, and spring, and no significant difficulties were encountered due to unrest. His health was good, and his appearance improved.

On June 9, 1933, the attendant noticed that the elephant took no interest in food or drink, and that he was standing with hind legs stretched backward. Later he sat on his haunches, and finally lay down on the left side. Dr. Knudson, upon examining the animal, noticed "some respiratory disturbance." At this time he would swallow oranges without masticating them. Fourteen of these were partially filled with aloes and administered. By the following morning marked purgation had been effected, and at 8 A.M. the elephant was standing and eating hay, apparently greatly improved. While thus engaged, he suddenly lay down on his left side, and after a few gasps he died. This was at 9:55 A.M., June 10, 1933.

*To Dr. Gust Knudson, Superintendent of the Woodland Park Zoo, and to the Seattle Park Board we are indebted for the specimen as well as most of the information concerning the history of this elephant.

Disputes as to ownership and responsibility for disposal delayed the autopsy, which was not completed until June 12, approximately forty-eight hours after death. There is no record of any of the organs having been weighed or described. The greater part of the carcass was taken to a fertilizer factory, the skin was placed in cold storage, where it has remained ever since, and the bones were preserved for mounting.

Fig. 2.—Interior of Tusko's left ventricle. Note the thick ventricular walls, the heavy papillary muscles, the leaflets of the mitral valve, and the chordae tendineae.

When the heart was removed from the thorax, the cavities were explored and emptied through the great vessels. A large, hard, irregular fibrin clot was removed from the left ventricle. This mass was grayish-white, friable, and irregular in outline. It was not attached to the walls of the chamber. The measurements of the clot were 15¾ in. (40 cm.) x 7 in. (18 cm.), and its weight was 34 oz. (966 gm.). The clot was preserved in alcohol. Three veterinaries who witnessed this examination

thought that the clot had formed ante mortem and was the cause of death, with probable embolism to the brain or some other vital organ.

Post-mortem degenerative changes were progressing rapidly when the heart was examined 48 hours after death. It had become flabby and almost black in color. The pericardial surfaces were all smooth and of silken texture. The chambers were empty of blood. Both coronary orifices easily admitted three fingers. The weight was 48 pounds and 4 ounces (21.9 kg.). The specimen was embalmed with formalin by injec-

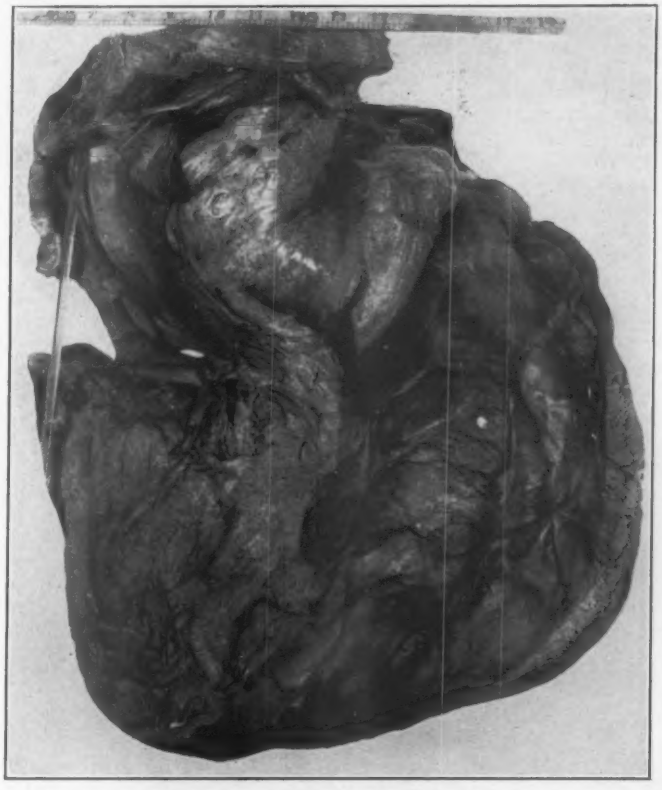

Fig. 3.—Interior of Tusko's right ventricle. Note the thinner muscular walls and lesser degree of papillary muscle development as compared with that of the left ventricle (Fig. 2). The chordae tendineae have been severed and the endocardium removed from the lateral portion of the ventricle. The broad leaflets of the tricuspid valve are seen at the upper left. Cross-section of a coronary artery appears at the extreme upper left.

tion of the coronary arteries under pressure of gravity; however, about one-fourth of the muscle mass could not be penetrated by the solution. It was then placed in a solution of formalin *in toto* and left for several months.

Examination of the heart by one of us (King) was completed in November, 1933. Post-mortem changes had obviously advanced to a moderate degree before embalming. There were a number of soft friable

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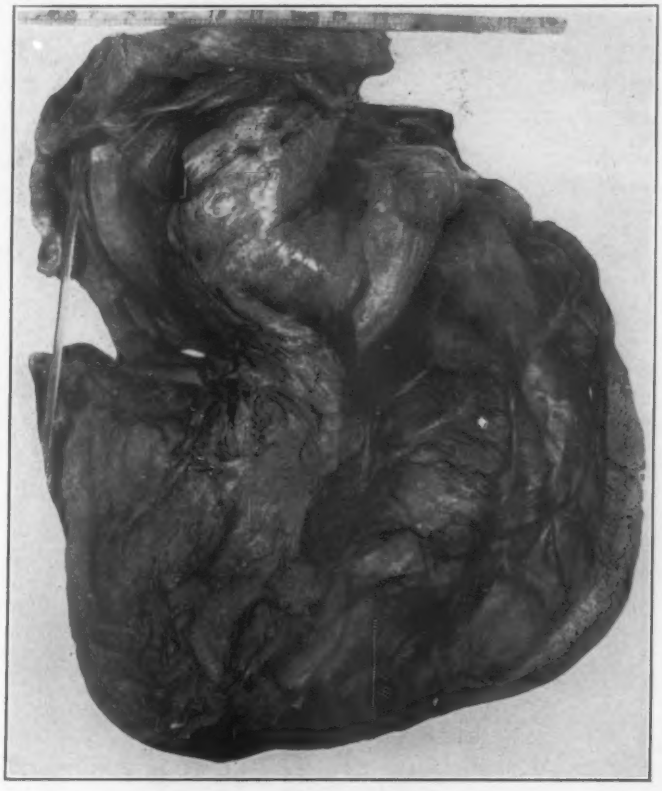

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Examination of the heart by one of us (King) was completed in November, 1933. Post-mortem changes had obviously advanced to a moderate degree before embalming. There were a number of soft friable

areas in each ventricle where the preservative had not penetrated. The pericardium appeared normal. There was no apparent hypertrophy or dilatation of the ventricles, and there was no sclerosis of the aorta or coronary vessels.

The exterior surface of the entire right ventricle was covered with a subepicardial layer of fat varying from 1 to 2 cm. in thickness. The borders of this fat were sharply defined at the interventricular sulci,

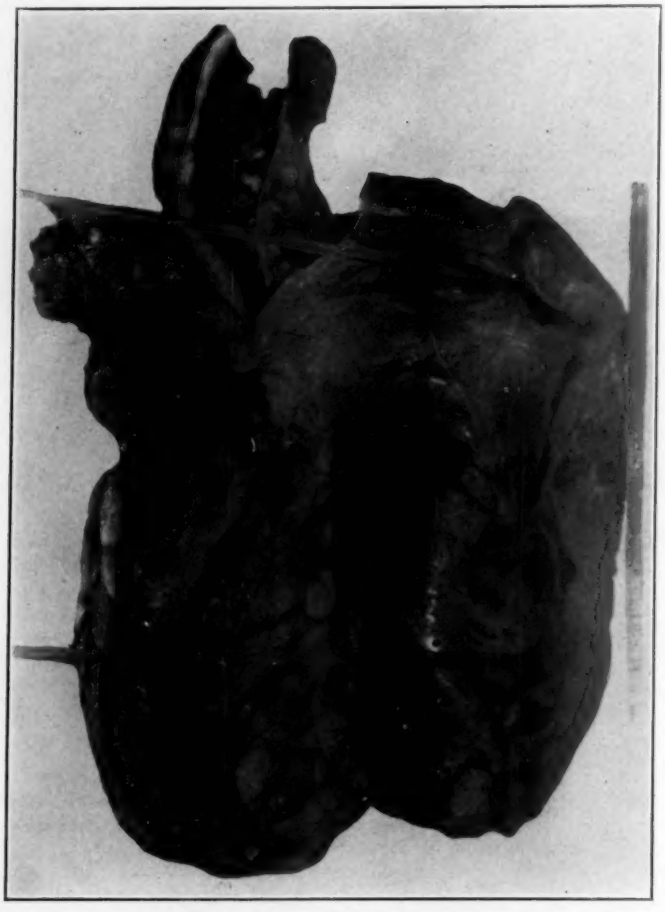

Fig. 4.—Interior of Tusko's left ventricle and left auricle. Note the walls of the aorta above.

which it filled. This layer of fat was continuous with that filling the coronary sulci. Removal of the fat at the apex of the heart revealed the bifid appearance described by others. Fat was conspicuously absent from the surface of the left ventricle.

The endocardium appeared normal and overlaid a very thin layer of fatty tissue. The valves were of normal structure and apparently competent. The edges of the leaflets were smooth and presented no evidence

of sclerosis. The chordae tendineae and papillary muscles presented no evidence of excessive fibrous tissue deposit. For views of the interior of the ventricles see Figs. 2 and 3.

The left coronary artery originated from the apex of a funnel-shaped left ventral sinus, which admitted three fingers. The first portion passed for a short distance between the pulmonary artery and the left auricle. It then divided into its two terminal branches, the interventricular and the circumflex arteries.

The origin of the right coronary artery was from the right ventral sinus, which was less funnel shaped and shallower than the left. The first portion was in close relation to the aorta and then extended along the coronary sulcus, partially encircling the right auricle, giving rise to several small branches along its course. At the posterior interventricular sulcus it terminated in a descending interventricular branch and a smaller transverse branch. The latter crossed the posterior sulcus and terminated in branches to the basal portion of the left ventricle. We did not find a third, or *atrial,* artery arising from the aorta as described by Hill.[2]

The muscular wall of the left ventricle was thicker than that of the right. The average thickness of the interventricular septum was greater than that of either of the lateral walls (Table III).

TABLE III

MEASUREMENTS OF HEART (TUSKO)

Weight of heart	21.9	kg.	(48¼ lb.)
Outside circumference of aorta (22 cm. from semilunar valves)	23.0	cm.	
Average thickness of wall of aorta	1.52	cm.	
Average thickness of wall of pulmonic artery	1.3	cm.	
Average thickness of wall of left ventricle	4.08	cm.	
Average thickness of wall of right ventricle	2.05	cm.	
Thickness of interventricular septum	6.0	cm.	
Circumference of mitral valve	36.9	cm.	(14½ in.)
Circumference of tricuspid valve	38.1	cm.	(15 in.)
Circumference of aortic valve	27.9	cm.	(11 in.)
Circumference of pulmonic valve	22.9	cm.	(9 in.)
Diameter of left coronary artery			
At orifice	2.0	cm.	
Interventricular branch	1.2	cm.	
Diameter of right coronary artery			
At orifice	2.0	cm.	
Circumflex portion	1.5	cm.	

The aorta and pulmonary artery were soft and elastic, the wall of the former being almost twice as thick as that of the latter. There was no evidence of sclerosis or calcium deposit in either.

The sinoauricular node measured approximately 1 x 2 cm. The auriculoventricular node, the bundles, and the Purkinje system could not be clearly outlined on account of the degenerative changes. Measurements

of the interior of the heart, made in November, 1933, approximately five months after death, were as given in Table III.

Histologic study of the muscle, valves, aorta and neuromuscular tissue was attempted but was unsuccessful on account of degenerative changes. The only detail of structure discernible was that the cells were of large size and contained nuclei of corresponding size.

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ADDENDUM

In a very recent paper, his second on studies of the cardiac anatomy of the elephant (II. The Heart and Great Vessels of a Foetal Asiatic Elephant. Ceylon J. Sc., Section B, Zoology and Geology, **21**: 45, 1938), W. C. Osman Hill found that the fetal heart (slightly older than midterm) described in this latest contribution agrees in all essential particulars with the hearts of adult animals of the Asiatic species.

"Its study has resulted in the emergence of further evidence regarding the very primitive nature of the organ, to the extent that it can definitely be stated that, in this advanced fetus, the heart, and related parts of the circulatory system, are in a state of development similar to that found in a human embryo of the fifth week of intrauterine life. Moreover, most of the embryonic characters in the proboscidean heart are known to be retained even in adult life, at least in some degree. Among the primitive features concerned are factors relating to form, shape and structure, and special attention may be directed to (i) the great transverse breadth of the organ relative to its other dimensions, (ii) the relatively large size and globular form of the ventricles, (iii) the apical bifurcation, (iv) certain arrangements in the interior of the right atrium, (v) the absence or incipient nature of the atrial appendages, and (vi) the poor differentiation of the papillary muscles.

"Besides these primitive features in the heart itself, a number of others, connected with more distal parts of the circulatory system, demand attention. Such are (i) the close connection of the systemic and pulmonary aortae, (ii) the simple curved form of the 'descending' aorta, (iii) the mode of branching from the transverse

part of the systemic aorta, (iv) the presence of a left precaval vein, (v) the disposition, etc., of the postcaval vein, and (vi) the arrangement of the azygos system of veins.

"(2) The atrial artery would appear to be a constant structure on the heart of the Asiatic elephant, having now been recorded in two adults, as well as in the fetus. There seems to be some variation in its mode of origin, but its distribution is much the same in all cases. Ideally this vessel takes the largest share in the formation of a more or less complete arterial ring which surrounds the roots of the great arterial stems as they emerge from the heart. The ring is completed ventrally, as far as it can be said to be complete, by the arch formed from the infundibular branches of the right coronary and ventral interventricular arteries. These last two vessels were not demonstrable in the fetal heart, but are well developed in the adult. They do not, however, form a complete arch, as they do on the human heart, for they form no precapillary anastomosis."

THE ELECTROCARDIOGRAM OF THE ELEPHANT*

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FRANCIS G. BENEDICT, PH.D., BOSTON, MASS.

IN THE course of a study of the physiology of the elephant an opportunity presented itself in the spring of 1936 to obtain a series of electrocardiograms from a number of circus elephants during their visit to Boston. Although the determination of the heart rate under different conditions was the primary reason for taking the electrocardiograms, the tracings themselves proved of such interest that they have been made the subject of the present report. Data on the elephant's heart rate have been published a number of times in the past.[1, 2, 3] Benedict and Lee[3] found that the rate averaged close to 40 per minute, with a normal range from 30 to 50, and occasionally was less than 30 or exceeded 50; the rate in a given elephant tended as a rule to be slightly lower when the animal was in the standing position than when recumbent (perhaps because the animal is more comfortable when standing, or because that position facilitates blood flow), although there were frequent exceptions due to various stimuli, such as noise or other commotion.

In 1921 Forbes, Cobb, and Cattell[4] took an electrocardiogram of a circus elephant that was visiting the Children's Hospital in Boston. The tracing they obtained was unsatisfactory because of the high resistance of the elephant's hide, the very small complexes of the record itself, and the high speed of the camera, which had been used for electromyography. However, a skillful reconstruction of their electrocardiogram, so that it conforms in amplitude and in timing to the usual standards, allows us to make a direct comparison with our own tracings. The heart rate of the elephant studied by Forbes, Cobb, and Cattell averaged 41, the duration of systole as measured by the interval from the beginning of Q to the end of T was 0.6+ second (the end of T was made out with difficulty), the QRS wave duration was about 0.15 sec., and the P-R interval was about 0.35 sec. These measurements are in fairly close agreement with our own.

Present Series.—During May, 1936, when the Ringling Brothers Circus was performing at the Boston Garden, one or more electrocardiograms were obtained by string galvanometer or by cardiette (mirror type galvanometer with amplifier) from each of the following nine elephants: Juno, Modoc, Tillie, Myrtle, Lizzie, Clara, Queen, Pigmy, and one unknown. The electrodes consisted of thin German silver plates covered with large cloth pads saturated in concentrated salt solution. The elephants were induced to step on these pads, which were simply laid on the cement floor over rubber mats. When the elephant was lying down,

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the pads were applied to the bottoms of the feet by an assistant. Because of the docility of the elephants, less difficulty than might have been expected was experienced in making connections. Remarkably low resistances (all well below 1,000 ohms and frequently in the neighborhood of 200 or 300 ohms) were invariably obtained from this procedure. Lead I was taken in all cases and often repeated; Leads II and III were occasionally taken also. The curves were sometimes smooth but more often slightly irregular in the base line, rendering it somewhat difficult to demarcate accurately the beginnings and endings of a number of the complexes which were themselves often not at all sharp. An example of the

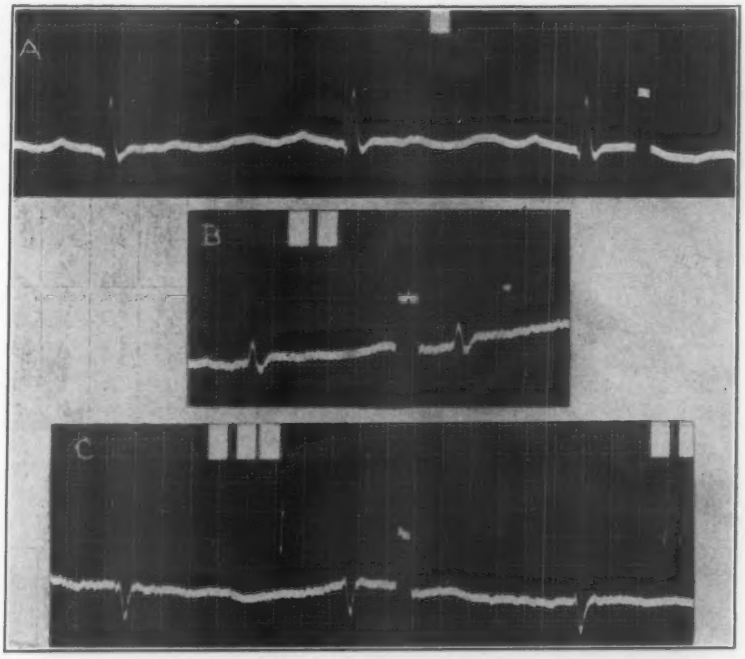

Fig. 1.—Electrocardiograms of the three classical leads of elephant Modoc. Time intervals, as also in Figs. 2 and 3: 0.2 and 0.4 sec. Amplitude: 10 spaces = 1.0 millivolt.

three leads of Modoc is shown in Fig. 1 and records of Lead I of Clara, Lizzie, and Juno are shown in Fig. 2.

Table I gives a description of the individual complexes and time intervals studied and measured in the best tracings of the nine elephants named above. It will be of interest and value to summarize the main features herewith.

P-Wave.—The P-waves of the elephants' electrocardiograms were invariably of low amplitude and were best marked in Lead I, which is in contrast to the findings in human electrocardiography with the subject in the sitting position. The amplitude in Lead I averaged about 0.1 millivolt (1 mm. excursion) with limits of 0.5 and 1.5 mm. In Lead II the P-waves tended to be flat, and in Lead III, slightly inverted.

TABLE I

DETAILS OF ELECTROCARDIOGRAMS OF ELEPHANTS (TIME INTERVALS IN SECONDS)

SUBJECT	LEADS	P-WAVE	P-R INTERVAL	QRS WAVE	Q-T TIME	T-WAVE	AXIS DEVIATION	RATE PER MINUTE
Modoc	I	Low, long domed	0.39	Small Q and S, R = +8. Dur.* = 0.18	0.62	Very low and long	Slight left	37.5
	II	Low, long domed		Small R and S. No Q		Flat		
	III	Flat		Small R, larger S		Sl. inverted		
Modoc	I	Higher, 1½ mm.	0.33	Q = –1, R = +8, S = –3, wide. Duration = 0.18	0.62	Higher, 1½ mm.		38
Modoc	I	Low, 1 mm.	0.38	Same. Dur. 0.18	0.64	Same		34
Modoc	I	Same	Same	Same		Same		Same
Tillie	I	Low, 1 mm.	0.37	Wide, monophasic R. R = 9 mm. Dur. = 0.16	0.60	Very low, sl. diphasic down and up		42
Tillie	II	Very low = ½ mm.	0.36	+3. Dur. = 0.13	0.70	Very low, late dome		36
Myrtle	I	+1½. Dur. = 0.16 and then flat 0.20	0.36	+4–½. Dur. = 0.12	0.60	Low, late dome, +1 mm.	Slight left	34 up and awake
Myrtle	I	–½ + 1. Dur. 0.16	0.40	+4. Dur. = 0.12	0.76	Sl. inverted –½		28 asleep
Juno	I	Low, 1 mm. Dur. = 0.2	0.36	–½ +8–2. Dur. = 0.16	0.79	+1 –0 +2. U present		26
Juno	I	Low, 1 mm. Dur. = 0.2	0.36	+8–2. Dur. = 0.16	0.76	+½–0 +2		24
Clara	I	Low, ½ mm. Dur. = 0.2	0.36	+5–2. Dur. = 0.12	0.60	Low late, 1 mm.		35
Pigmy	I	Very low, +½ mm.	0.28	+4–1. Dur. = 0.14	0.60	Very low, +½ mm.		39
Queen	I	Low +½-1. Dur. = 0.2	0.36	+8–1. Dur. = 0.15	0.68	S-T sl. sagging, low late T = 1	Slight left	36
Lizzie	I	Small early, +½-1. Dur. = 0.12	0.41	+7-2. Wide S. Dur. = 0.18	0.72	Sl. S-T sag, sl. late dome, ½		33
Lizzie	I	Same	0.35	Same	0.59	Same and followed by U-wave		53
Unknown	I	+1	0.38	–1 +8. Dur. = 0.14	0.65	Domed +1 mm., flat, sl. inverted	Slight left	33
	II	Small		+3				
	III	Flat		–8 +2				

*Dur. = duration.

The shape of the P-waves was as a rule that of a low dome or blunt peak, at times slightly diphasic with a very small early dip before the rise.

The duration of the P-waves ranged from 0.12 to 0.20 sec., averaging 0.16 sec.; after the end of P the baseline remained level for about 0.20 to 0.25 sec. before the onset of the QRS waves.

There was little change in amplitude, shape, or duration with varying heart rates although there were not enough records at different rates in any one animal to draw clear conclusions concerning this point.

P-R Interval.—The P-R intervals ranged from 0.28 to 0.41 sec., averaging 0.36 to 0.37 sec. In one animal (Lizzie) the interval varied with

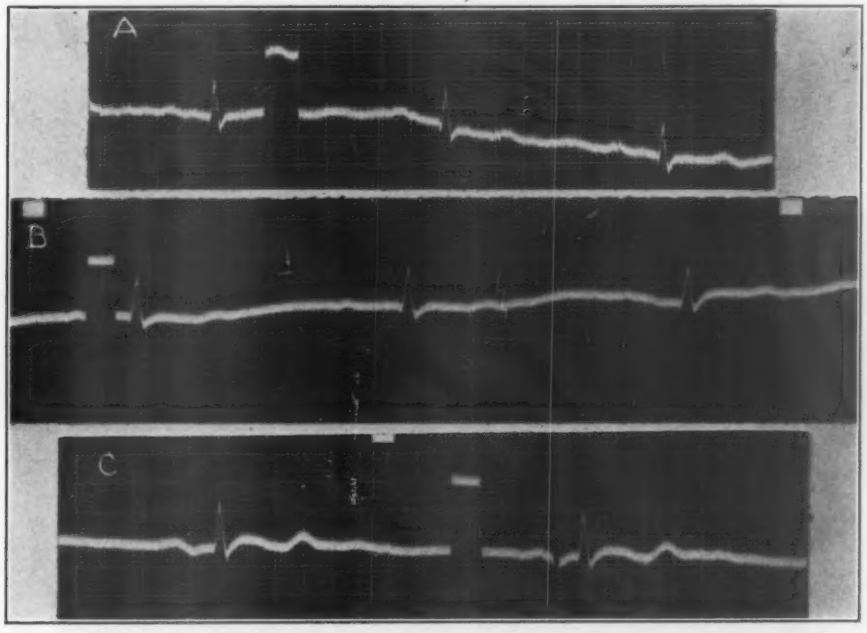

Fig. 2.—Electrocardiograms of Lead I of three elephants, Clara, *A*, Lizzie, *B*, and Juno, *C*, respectively.

the heart rate, as might be expected; it was 0.35 second with the unusually rapid heart rate of 53, and 0.41 sec. at a rate of 33.

QRS Waves.—The QRS waves, like the P-waves, were invariably of greatest amplitude in Lead I, in which the R-wave averaged about 6 to 8 mm. and the S-wave 1 to 2, with or without a very small Q wave (usually present). The S-wave in Lead I was often, in fact generally, the widest part of the complex.

The duration of the QRS wave was 0.16 sec., on the average, with a range from 0.12 to 0.18 sec. There seemed to be no relation of the QRS duration to heart rate.

In Leads II and III the QRS waves were always smaller than in Lead I; they were largely upright in Lead II and usually inverted in Lead III.

Thus there was, in the four animals from which three leads were obtained, consistent evidence of slight left axis deviation.

S-T Segments.—The S-T segments varied somewhat from animal to animal, averaging, however, little or no deviation from the zero base line. At times there was a slight convexity and at times a slight concavity, but often a straight line. The take-off from the QRS waves was neither high nor low.

T-Waves.—The T-waves were as a rule late, low, and of greatest amplitude in Lead I, where they varied from +0.5 to +2.0 mm. In Lead II they were low or flat, and in Lead III flat or very slightly inverted.

The shape of the T-waves was generally that of a long dome, rarely that of a sharper peak. At times they were slightly diphasic with an early sagging. In one case (Myrtle, see Fig. 3), the T-waves in Lead I

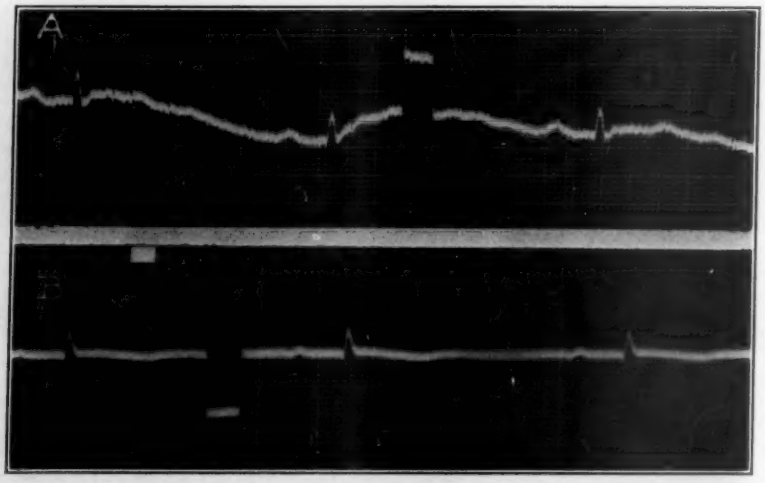

Fig. 3.—Electrocardiograms of the first lead of elephant Myrtle. *A*, standing, awake. *B*, lying down, asleep.

changed from late, low, dome-shaped elevations (1 mm. high) when the animal was standing and awake, to long, slightly inverted, troughlike depressions (0.5 mm. deep) when the animal was lying on her side asleep; the P-waves and to a less extent the QRS waves were also lower in the record taken with the animal recumbent. A change in heart position relative to the electrodes was probably primarily responsible for these electrocardiographic changes.

In a few records small U-waves followed the T-waves.

Q-T Times.—The duration of systole, as measured by the time interval from the beginning of Q to the end of T, varied from 0.59 to 0.79 sec., averaging 0.65 sec. It varied with the heart rate, as would be expected; thus the shortest Q-T time (0.59 sec.) was found in Lizzie when her heart rate was 53, the fastest encountered in the present series of records, while the longest Q-T times (0.76 to 0.79 sec.) were found in the only

two elephants whose records showed heart rates below 30 (0.76 second in the case of Myrtle with a heart rate of 28, and 0.76 and 0.79 sec. in the case of Juno whose rate was 24 to 26). Lizzie's Q-T time varied from 0.59 sec. at a heart rate of 53 to 0.72 sec. at a rate of 33.

DISCUSSION

The points of particular interest in the foregoing analysis of electrocardiograms of circus elephants are (1) the relatively low amplitude of all the complexes (P-, QRS, and T-waves) in the three classical leads, with greatest excursion in Lead I, and (2) the unexpected length of the various time intervals (P-R interval, QRS wave, and duration of systole as measured from the onset of the QRS wave to the end of the T-wave).

Neither artifact nor disease can explain the low amplitudes which are evidently characteristic of elephants' electrocardiograms. Although it is possible that there is a fairly close balance of electrical potential in the heart muscle at all times, it is more likely that the small difference of potential is due to the long distances of the heart mass itself from the junctions of the legs to the trunk; comparably, it is well known that in man an electrocardiogram taken from lead points on the legs shows very small complexes.

Some of the undue length of the P-R interval and Q-T time might be ascribed to the bradycardia, but the delay is out of all proportion to the heart rate if we compare the findings in human electrocardiography at such slow rates of contraction; in man with sinoauricular bradycardia at a rate of 40 the P-R interval might normally be 0.2 sec., but never nearly double that, as in the case of the elephant, and the Q-T time in man at a heart rate of 40 might be 0.4, or even 0.45 sec., but never as great as 0.6 to 0.7 second as in the elephant. It would appear that the great size of the elephant's heart may best explain the P-R interval and Q-T time as well as the unusual width of the QRS wave (0.1 to 0.2 sec). It is important to note that, as described by King, Burwell, and White,[5] the heart muscle, nodal tissue, and Purkinje network are the same as in other herbivorous mammals.

SUMMARY

An analysis has been made of the electrocardiograms of nine circus elephants with heart rates ranging from 24 to 53 per minute (average of 35 to 40).

Relatively low amplitude of the P-, QRS, and T-waves was found in the three classical leads (with greatest excursions in Lead I), despite accurate standardization which was made easy by the remarkably low resistance invariably found (often only 200 to 300 ohms in any given lead).

The various time intervals (P-R of 0.28 to 0.41 sec., QRS of 0.12 to 0.18 sec., and Q to T time—duration of systole—of 0.59 to 0.79 sec.) were

beyond the measurements to be expected at slow heart rates in the case of mammals of average size like man, and may be explained by the immense size of the elephant's heart with its longer paths of impulse conduction and its greater bulk of contracting muscle.

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Department of Clinical Reports

PERFORATION OF THE INTERVENTRICULAR SEPTUM CAUSED BY CORONARY OCCLUSION

Report of a Case

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PERFORATION of the interventricular septum is an uncommon complication of coronary occlusion. To date twenty cases in which its occurrence has been verified have appeared in the literature. Of these only three have been diagnosed correctly ante mortem (Brunn,[1] Sager,[2] and Stanley[3]). It is our purpose to report the fourth case to be diagnosed before death and to point out that Sager has set forth criteria which if borne in mind will lead to accurate diagnosis in a higher percentage of cases.

CASE REPORT

Mrs. M. B. J., a widow, aged 70 years, first came to us on Jan. 14, 1938, because of a tracheitis of several weeks' standing. Examination of the heart at that time showed nothing abnormal. The blood pressure, however, was 160/100.

On the morning of Jan. 19, 1938, the patient was awakened by a severe, devastating pain between the shoulder blades, radiating down both arms, to be followed a bit later by distress over the lower precordium. When first seen by us at 11:00 A.M. of the same day, severe pain had persisted and was accompanied by sweating. She was obviously very ill. The pulse rate was 96 per minute, the blood pressure 190/110. The heart sounds were muffled. One 1/100 of a grain of nitroglycerin under the tongue gave some relief from the precordial pain but that between the shoulders was unaffected. Both pains finally yielded to morphine sulfate hypodermically, first in the dose of ¼ grain and somewhat later, one ⅛ grain. On the evening of the day of onset the blood pressure had dropped to 140/90. At noon the temperature per rectum was 100° F. On the morning of January 20 the pulse rate was 120, the blood pressure 100/80. The heart had enlarged to the left at the apex. There was a faint apical systolic murmur and gallop rhythm had appeared. Moist râles were found at both bases. At midnight the rectal temperature was recorded at 103.6° F. The patient vomited repeatedly and intermittently suffered pain between the shoulder blades. Prostration was an outstanding symptom and increased as time went on. On the third day, January 21, the patient was much worse. The blood pressure was now 88/74. Tachycardia developed and ranged from 120 to 158 with many premature contractions. Quinidine sulfate, in doses of 3 grains every four hours, was started to forestall the development of ventricular fibrillation. Gallop rhythm persisted. The rectal temperature was constantly elevated and ranged from 102.2° to 102.8° F. Laboratory data were

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as follows: The hemoglobin was 83 per cent (12.5 gm. per cent); the erythrocyte count, 4,460,000; the leucocyte count, 11,300; and the differential leucocyte count showed 76 per cent polymorphonuclears (lobulated 67 per cent and band forms 9 per cent). The sedimentation rate was 55 mm. in one hour (Wintrobe Normal 0-20.) An electrocardiogram (Fig. 1) confirmed the initial clinical impression of acute coronary occlusion but did not definitely place the site of infarction, though it suggested a lateral wall involvement (Lead IV was made with the right arm lead at the apex and the left arm lead over the left side of the chest posteriorly). On January 22, the fourth day of the illness, the patient showed considerable improvement. She was no longer bothered by pain. Vomiting ceased. The rectal temperature was lower (100.4° to 101.6° F.). The pulse rate slowed to 100 and the blood pressure increased to 100/80. Satisfactory progress continued. On the seventh day, January 25, the rectal temperature ranged from 99.6° to 100.2° F., the

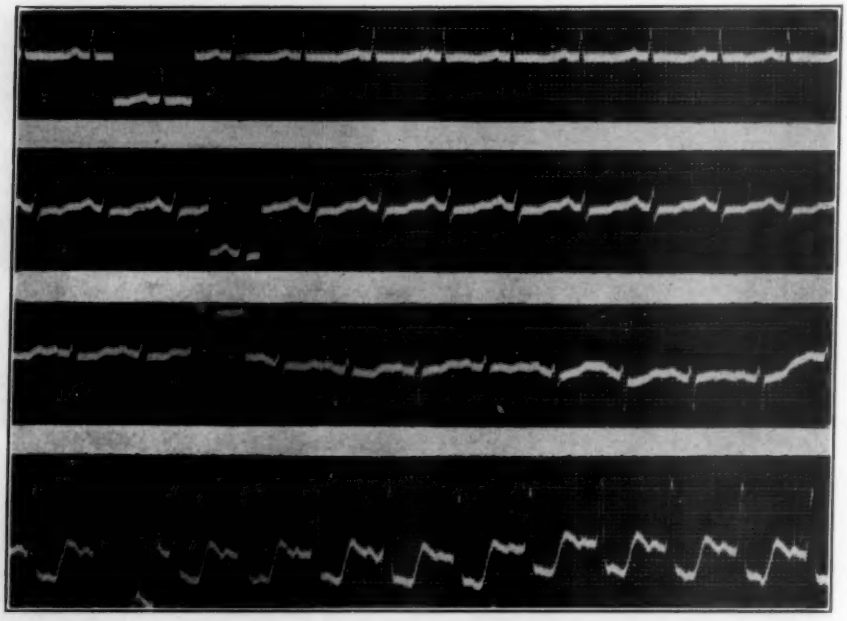

Fig. 1.—Electrocardiogram made on the third day of the illness. Lead IV is inscribed from anterior and posterior chest connections, according to the old technique. See text for interpretation.

pulse rate from 90 to 100, and the blood pressure in the morning was 105/70. However, at 5:00 P.M. she complained of return of the precordial pain and oppression as well as pain under the left shoulder blade. Intermittently during the night she was nauseated and at 9:00 P.M. she vomited. All of the symptoms and particularly the pain were mild in comparison with those suffered at the time the occlusion developed. Examination the next day, January 26, revealed important changes, and in view of subsequent findings it is necessary to describe the situation in some detail. The patient was free of pain, complaining only of marked weakness. No increase in dyspnea or cyanosis was noted. There was no engorgement of the neck veins. The pulse was 112 to the minute, regular, but of fair quality only. The blood pressure had dropped to 88/68. There was no apparent increase in the heart size to the left. Unfortunately, the limits of the right border were not determined at this time. No thrills could be palpated at any point. Most remarkable were the auscultatory findings. Over the entire precordium there was

a loud, high-pitched, blowing systolic murmur, most intense in the left parasternal region in the fourth and fifth intercostal spaces, where the murmur was slightly rasping in character. Transmission was wide both to the left and to the right and even into the back and epigastrium but the intensity of the new murmur was by far most marked toward the apex and the left axilla. The second heart sound was faint and in many of the cycles there was a protodiastolic gallop rhythm. No murmur could be heard in diastole. The obvious changes in the picture were ascribed to spontaneous rupture of an infarcted interventricular septum. Bedside notes made during the next four days indicate that there were no radical changes in the patient's circulation. The fact that there were less dyspnea and fewer râles suggested that pulmonary congestion was diminished. The rectal temperature level was practically stabilized at 100° F. The blood pressure ranged from 80/60 to 92/75, and the pulse pressure from 17 to 20. On January 31, six days after the perforation, the edge of the liver had descended to a point 5 cm.

Fig. 2.—Photograph of the heart. The arrow points to the perforation of the interventricular septum. See description of pathologic findings.

below the costal margin, and on the next day, 8 cm. Administration of digitalis was followed by temporary lessening of hepatic congestion. On February 6, twelve days following the perforation, edema appeared over the lower part of the back. The course thereafter was one of increasing congestive failure. Death ensued on February 12, fifteen days after the perforation and on the twenty-fifth day of the illness.

NECROPSY OBSERVATIONS CONCERNING THE HEART AND AORTA*

There was a rather diffuse thickening of the aortic wall for the first few centimeters, above which point scattered, nodular, atheromatous patches, occasionally calcified, were more evident.

The coronary orifices were patent, measured about 1.5 to 2 mm. in diameter, and were surrounded by a firm ring of somewhat pouting fibrous tissue. The aortic cusps were definitely thickened by fibrosis in the proximal one-third to one-

*By Dr. J. W. Lindsay, Pathologist.

half. The outer edges were thin and the valves appeared to be quite competent. The endocardium of the left ventricle was somewhat thickened as indicated by its slight spasticity. Yellowish plaques and dots were seen in the papillary muscles and scattered diffusely through the myocardium. A large area of evidently degenerated muscle, mottled in color and rough in appearance, was noted in the interventricular septum, in the upper border of which a perforation measuring 1 by 0.5 cm. was observed. On dissection of the left coronary artery, which was found to be markedly calcified, there were several fairly large branches penetrating to the border of the area of degeneration described. While the right coronary artery was patent for a greater distance than the left, it also was markedly nodular and fibrosed, and the posterior descending branch was completely occluded in the neighborhood of the degenerated area of the septum. The wall of the right ventricle was much thinned and the changes in the musculature, while similar to those in the left ventricle, were not so evident. All valves showed some degree of sclerosis though all appeared to be competent.

SUMMARY

This is a report of the twenty-first case of perforation of the interventricular septum caused by coronary occlusion in which the presence of this lesion was verified, and the fourth in which a correct diagnosis was made ante mortem.

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Department of Reviews and Abstracts

Selected Abstracts

Hessel, G.: Concerning Renin. Klin. Wchnschr. 17: 843, 1938.

The author has obtained Tigerstedt's renin in a yellow amorphous powder pure enough for 0.1 mg. to give a good rise of pressure (40 mm. Hg) in a 9 kg. dog. It was obtained by pressing out the juice of hog kidney (also beef, dog, cat, and rabbit), dialyzing it against running water, which rid it of depressor effects, and precipitating it during a period of a day in acetic acid solution (pH 4.4) saturated with sodium chloride. The salt was then dialyzed off, the pressor substance dissolved in 2 to 5 per cent sodium chloride solution and filtered; filtrate was acidified with lactic acid (pH 3.4); and the substance adsorbed on kaolin, from which it was freed by making the solution faintly more alkaline than other adsorbed substances. The renin was then freed from pigments and electrolytes by ultrafiltration and dried in an evacuated desiccator. It is soluble in water and weak sodium chloride solution, insoluble in and destroyed by organic solvents. It is also destroyed by mineral acids and alkali, by heating to 65°, and by pepsin or trypsin. Its molecular weight is high, it is not dialyzable and is precipitated by concentrated salt solutions, and gives protein reactions.

The rise in arterial pressure which follows intravenous injection of 0.2 or even 0.1 mg. is slow (maximum in 2 to 5 min.) and takes from 15 to 60 minutes to subside. It does not affect heart rate, and the author states that it does not increase the amplitude of the pulse. However, in the only optical record shown, the pulse pressure increases roughly 10 mm. Hg, as is to be expected. It does not affect the isolated heart, the iris, bronchial muscle, or uterus. The marked differences in action between renin and other pressor substances (tonephin, vasopressin, tyramin, adrenalin) are well shown in several records.

The author has obtained continuous hypertension in rabbits by daily injections of renin over a period of five weeks—a hypertension which persisted as long as seven months after discontinuing the injections.

He also shows two records of a rise of blood pressure (20 mm. Hg) in dogs following the injection of 3 c.c. of blood from the renal vein of a dog's kidney, the artery to which had previously been partially clamped.

STEELE.

Jochim, Kenneth: The Contribution of the Auricles to Ventricular Filling in Complete Heart Block. Am. J. Physiol. 122: 639, 1938.

From ventricular volume curves recorded simultaneously with aortic pressure pulses in a dog with complete A-V block, an analysis is made of the dynamics of each auricular beat. The effective auricular contribution to ventricular filling is defined and its magnitude correlated with the A_s-V_s interval. The effective auricular contribution is found to increase slowly as the A_s-V_s interval decreases. When this interval becomes equal to the duration of auricular systole, the auricular contribution begins to increase rapidly, reaching a maximum at an

A_s-V_s interval equal to about half the duration of auricular systole, and falling off sharply to zero as the interval further decreases. The factors affecting this correlation are discussed.

AUTHOR.

Katz, L. N., and Kolin, A.: The Flow of Blood in the Carotid Artery of the Dog Under Various Circumstances as Determined with the Electromagnetic Flowmeter. Am. J. Physiol. 122: 788, 1938.

A method is described for measuring cyclic variations in the velocity of blood flow in unopened blood vessels based on the induction of an E.M.F. in the blood when moving through a magnetic field. Cyclic variations in the velocity of blood flow through the carotid artery of anesthetized dogs were recorded with this D.C. method under various conditions, viz.: 1, with the anesthetized animal intact; 2, with the chest opened; 3, during rapid saline infusion; 4, during partial occlusion and after release of the thoracic aorta; 5, during aortic valve insufficiency in which an early diastolic back flow was demonstrated; 6, during marked cardiac arrhythmia; 7, during ectopic beats, and 8, during gasping respiration. The characteristics of the velocity curves in each case are described and their significance discussed.

AUTHOR.

Corwin, Warren C.: Experimental Hypercholesteremia in Dogs. Arch. Path. 26: 458, 1938.

The data obtained from the experiments indicate that a diet high in fat may or may not produce moderate hypercholesteremia in the dog. Lecithin of adrenal origin, when given by mouth daily, will constantly raise the concentration of cholesterol in the blood. Lecithin plus a diet high in fat will effect marked elevation of the level of the blood cholesterol and of cholesterol esters. Cholesterol and sodium cholate have no effect when administered by capsule in the solid state.

If the development of arteriosclerosis in the dog is dependent on the development of hypercholesteremia, as in the case of the rabbit, the studies reported indicate that perhaps the dog may yet be employed in the study of this disease.

NAIDE.

Hsi-Chun Chang, Kuo-Fan Chia, Ching-Hsiang Hsu and Lim, R. K. S.: A Vagus-Post-Pituitary Reflex. I. Pressor Component. Chinese J. Physiol. 12: 309, 1937.

In dogs in which vascular connection with only the head exists, the neck having been crushed (no mention of periarterial sympathetic resection) and vagi cut, it is possible to produce a pressor response in the systemic circulation by stimulating the central end of the vagus or the cervical sympathetic nerves. Removal of the pituitary gland or cutting its stalk prevents the pressor response to central vagal stimulation but not to sympathetic stimulation. The authors conclude that stimulation of the vagus nerve calls forth secretion of posterior pituitary principle by that gland's secretory nerves which then acts on the systemic arterioles directly. This view is opposed to the notion that the vagus pressor effect is brought about through stimulation of a sympathetic center in the hypothalamus.

STEELE.

Sabathie, L. Gonzales: Phonocardiographic Studies of Reduplication of the Second Heart Sound. Rev. argent. de cardiol. 5: 25, 1938.

The phonocardiographic picture of the second heart sound simultaneously recorded with the venous and central arterial pulses in sixteen cases of mitral stenosis with clinical reduplication of the second sound and variable degrees of evolution and

cardiac failure (two of them with auricular fibrillation), and in nineteen persons with physiologic reduplication of the second sound (eleven children from 5 to 12 years of age and nine young adults from 15 to 30 years of age) and, finally, in five patients with organic heart disease, showing marked disturbances of intraventricular conduction, all of them presenting clinical reduplication of the second sound, revealed that in a case of mitral stenosis the reduplication was simulated by an opening snap of the mitral valve, and in two young people by a physiologic third heart sound. In the rest of the cases a true reduplication was confirmed.

In all cases of mitral stenosis and physiologic reduplication the first component of the second sound corresponded in time with the aortic incisura, showing that the aortic valves closed in advance to the pulmonary, a fact against Potain's views assuming that the opposite was the case in mitral stenosis, but in agreement with his views so far as physiologic reduplication is concerned.

In four of the five cases of ventricular asynchronism, the first component of the second sound coincided with the aortic incisura (aortic precedence) and in the fifth, a pulmonary precedence was recorded.

AUTHOR.

France, Richard: The Use of the Electrocardiogram in the Diagnosis of Adhesive Pericardio-Mediastinitis. Bull. Johns Hopkins Hosp. 63: 104, 1938.

An analysis has been made of thirty-eight cases in which shift of the electrical axis was studied during life, and the hearts were examined at autopsy. No constant relationship was found between the fixation of the electrocardiogram and the presence of restricting pericardial adhesions. It is, therefore, concluded that the electrocardiographic test for "axis shift" is not of value in the ante-mortem diagnosis of adhesive pericardio-mediastinitis.

AUTHOR.

Robertson, Sylvan, and Katz, Louis N.: Observations on Referred Pain of Cardiac Origin. Am. J. M. Sc. 196: 199, 1938.

A method was developed for inducing an anginal attack in susceptible patients with their permission. This was successful in nineteen out of twenty-four patients with definite clinical angina pectoris. It was not successful in producing an anginal attack in any of the fifty-five cardiac and "noncardiac" controls nor in any of the thirty-nine patients with doubtful clinical angina pectoris.

The method consisted of producing five-minute ischemia in the left arm by raising the pressure in a blood pressure cuff on the arm to 50 mm. Hg above systolic pressure. This cuff test was positive on the right arm and not on the left arm in three patients in whom the pain was referred to this arm.

The possible mechanisms involved are discussed. The ability to induce angina in this way serves to emphasize the neuropsychic aspects of the anginal attack and offers another cause for the variability in its occurrence.

AUTHORS.

Misske, B.: Renal Insufficiency and "Pale" Hypertension on the Electrocardiogram. Arch. f. Kreislaufforsch. 2: 267, 1938.

Fifty-three cases of uremia and fifty cases of nephrosclerosis without evidence of renal insufficiency were investigated to see whether electrocardiographic changes are due to arterial spasm of the coronary arteries or to uremic intoxication.

In uremia all cases showed evidence of myocardial damage in the electrocardiogram, and 41 per cent showed more than one electrocardiographic abnormality. The chief abnormalities were flattening or inversion of T, low "voltage," and

intraventricular block. In nine cases studied more intensively, some parallelism of electrocardiographic changes and changes in the degree of uremia could be found. Therefore, electrocardiographic changes are due to "myodegeneratio uremica."

KATZ.

Eckey, P., and Fröhlich, R.: Concerning Unipolar Leads for the Electrocardiogram. Arch. f. Kreislaufforsch. 2: 349, 1938.

To obtain true unipolar leads the subject was immersed in distilled water bath contained in a wooden bathtub lined with copper. The subject lay on a wooden lattice with the head under water, the nose closed, and breathing through a glass tube. A copper lid was then placed over the patient and the indifferent electrode placed on this lid. It was shown that while Wilson's central terminal and Molz's copper mat were both not nul points, Wilson's central terminal approached the true nul point, showing deviation during the heart cycle of 0.2 to 0.3 millivolts.

KATZ.

Eckey, P., and Schäfer, E.: Deformation of the Ventricular Complex of the Human Electrocardiogram by the Action Currents of Abnormal Conducting Fibers. Arch. f. Kreislaufforsch. 2: 388, 1938.

A case is reported of an apparently normal patient with intermittent periods of beats with short P-R and prolonged QRS complexes. By algebraic subtraction of the normal QRST from the abnormal one, a small ventricular complex was obtained having its T-wave opposite to the broad QRS. This the author attributes to the action current generated in abnormal conducting tissue during the abnormal beats and believes this explains the peculiar type of record obtained.

KATZ.

Parkinson, John, Bedford, D. Evan, and Thomson, W. A. R.: Cardiac Aneurysm. Quart. J. Med. 7: 455, 1938.

The evolution of our knowledge of cardiac aneurysm and its morbid anatomy is shortly reviewed.

Cardiac aneurysms are usually due to coronary occlusion with resultant infarction, and rarely to syphilis, infective endocarditis, congenital defects, or trauma. A detailed necropsy report is given of a case ascribed to rheumatic necrosis of the myocardium.

Cardiac aneurysms, like infarcts, involve the left ventricle almost exclusively and may best be classified as anterior or posterior, according to the coronary branch occluded. The great majority involve the anterior wall of the left ventricle, usually at or near the apex.

The clinical and radiologic features of fifteen cases of cardiac aneurysm are described, and in five of them the diagnosis was confirmed by necropsy. The significant clinical features are a history of coronary thrombosis, enlargement of the heart to the left, a normal or low blood pressure, distant heart sounds, and an electrocardiogram most often indicative of anterior infarction (T_1 type). Expansile pulsation separate from the apex beat, or an extensive area of precordial pulsation, is rare but suggestive sign.

Diagnosis depends mainly upon radiologic examination. Anterior aneurysms cause enlargement of the heart to the left, with deformity of its contour. This deformity, seen from the front, may take the form of (1) broadening of the apex or angulation of the left border, giving the heart a square or rectangular appearance;

(2) elongation of the heart to the left; (3) a diffuse bulge or, more rarely, a localized hump on the left border. In the right oblique position, "ledging" of the anterior heart border is of great diagnostic value. Posterior aneurysms are best seen in the left oblique position, and may displace the esophagus. Aneurysm of the interventricular septum has been known to cause enlargement of the heart to the right. Calcification of the aneurysmal wall, when present, is an invaluable sign. Radioscopy is essential to determine the optimum position for demonstrating the aneurysm, to observe the character of the pulsation, and to detect localized adhesion.

The differential diagnosis has to be made from an enlarged right ventricular conus, aortic aneurysm, especially that involving a sinus of Valsalva, calcified pericardium, loculated pericardial exudate or cyst, the para-apical triangle of fat, and from intrathoracic neoplasm or cyst.

AUTHORS.

Read, Frances E. M., Ciocco, Antonio, and Taussig, Helen B.: The Frequency of Rheumatic Manifestations Among the Siblings, Parents, Uncles, Aunts, and Grandparents of Rheumatic and Control Patients. Am. J. Hyg. 27: 719, 1938.

This paper reports on the frequency of the occurrence of rheumatic infection (chorea, acute rheumatic fever, and rheumatic carditis) in the siblings, parents, uncles, aunts, and grandparents of thirty-three white children with rheumatic disease and of thirty-three white nonrheumatic children selected as a control. The method of the collection of the material and of the verification of the information is given in detail. It is shown that the rheumatic and control groups do not differ materially with respect to the age distribution, sex composition, mortality rate, or in regard to the character and accuracy of the information.

Statistical analysis of the data indicates that rheumatic manifestations were found to have occurred in 15.5 per cent of the siblings of the rheumatic patients and in 4.0 per cent of the siblings of the control patients.

Among the parents of the rheumatic patients, 30.8 per cent were found affected, compared to 7.7 per cent among the parents of the control children.

Some form of rheumatic disease has occurred in 9.1 per cent of the uncles and aunts of the rheumatic children and in 3.8 per cent of the corresponding relatives of the control children.

The frequency of rheumatic disease is almost eight times as high among the grandparents of the rheumatic patients as among the grandparents of the control children, the percentages being, respectively, 18.2 and 2.3.

All these differences are statistically significant and are corroborated by a marked difference in the calculated attack rate based on the life experience of each group of relatives.

The high frequency of rheumatic disease found among the parents and siblings of rheumatic children confirms the numerous observations reported by others. A similar prevalence of rheumatic disease found among the uncles, aunts, and grandparents appears highly significant. Between the patients and their siblings and parents there is usually contiguity as well as consanguinity, but the uncles, aunts, and grandparents of the patients, in the majority of cases, do not belong to the same household or to the same immediate environment. Their necessary and known relation to the patient is not that of sharing a common environment but only one of consanguinity and of common inheritance.

These findings, although not sufficiently definitive to determine the relative importance of heredity and environment, are indicative of the strong familial tendency to this disease. The fact that such a familial tendency has been manifest for at least three generations is strongly suggestive of the existence of a constitutional susceptibility to this disease. This does not eliminate the possibility that exposure is also an important factor.

The facts here presented, while not conclusive, clearly indicate the need for a more thorough study of (1) the epidemiology of this disease, especially with regard to the sequence between cases in the same family, and (2) the inherited predisposition, including a search for stable somatic characteristics which might be associated with susceptibility to rheumatic infection.

AUTHOR.

Allen, E. V., and Adson, A. W.: Answers to Some Objections to Extensive Sympathectomy for Essential Hypertension. Proc. Staff Meet., Mayo Clinic **13**: 426, 1938.

An extraordinary interest in the treatment of essential hypertension by sympathectomy has developed. Concurrently with this interest, certain objections to the treatment of essential hypertension by sympathectomy have been broached. The objections most frequently stated are considered and answered for the purpose of clarification of the issues. Most of the theoretical objections have been shown not to be valid as far as humans are concerned by the results obtained following sympathectomy.

HINES.

Zinck, K. H.: Changes in Blood Vessels and Organs Following Burns. Klin. Wchnschr. **17**: 278, 1938.

Microscopic studies of the tissues of eight youthful subjects who died of third degree burns showed many interesting changes. Some of these changes are, as the author admits, well known. The author notes especially localized swellings of the larger arteries around the vasa vasorum, which appear within twenty-four hours and progress through atrophy of both the elastic and muscular coats to fragmentation within three weeks. The muscular coats of the venous walls also participate in the process, and even in the aorta is affected to a milder degree. The lesions recall those reported to follow extreme use of adrenalin in man. The heart also is involved partly by a similar affection of the coronary vessels and partly in an apparently independent process consisting of edema and fatty degeneration of the fibers, often with considerable destruction of the contractile substance. All of the organs and tissues show pathologic changes; swelling and rupture of the striated muscle fibers; replacement of the normal white cells of the blood by youthful cells of the myeloid series and shrinking of the red blood cells; in the kidney, inflation, collapse and lysis of the glomeruli; hemorrhage into the capsular spaces, cloudy swelling and hyalinization of the tubules, occasionally severe panarteritis but always widespread edema. Somewhat similar changes, mostly involving edema are found in all the organs. Of especial interest is the disappearance of lipoid from the adrenal glands and the disappearance of the basophilic substance and pepton cells of the pituitary gland. The author wonders whether these changes might not be of importance in the lack of regulation of blood pressure. In concluding, he states that many of the pathologic changes are similar to those of acute infections, notably diphtheria, and decries the use of cortical extract in treatment when it is obvious that the adrenal gland is only one of the many organs involved.

STEELE.

Mészáros, K.: Oscillometric Studies of the Arteries in Scleroderma. Acta med. Scandinav. **95**: 522, 1938.

Ten patients, suffering with scleroderma, uniformly showed decrease in the oscillometric index and in the more advanced cases, the curve was exceedingly

flat. Hot water baths (40° C.) did not increase the oscillometric readings, from which the author concludes that the elasticity of the arteries is decreased in this disease.

STEELE.

Whittaker, Louis D., and Pemberton, John deJ.: Mesenteric Vascular Occlusion. J. A. M. A. 111: 21, 1938.

In this series of sixty proved cases of mesenteric vascular occlusion, in thirty-six (60 per cent) the condition was unrelated to any surgical procedure and in twenty-four (40 per cent) it occurred following some surgical procedure. Surgical measures were resorted to in treatment of the occlusion in only nineteen cases (31 per cent) with a mortality rate of 84 per cent. The condition of the forty-one remaining patients precluded any hope of surgical intervention. Arterial occlusion occurred in nineteen cases (31.7 per cent), venous occlusion in twenty-seven cases (45 per cent) and combined arterial and venous occlusion in fourteen cases (23 per cent). Cardiac disease, hepatic or splenic disease, arteriosclerosis and acute abdominal infections were the predominant factors in the etiology of mesenteric vascular occlusion.

The symptoms were those of an abdominal emergency. Pain was the most common symptom and was more sudden and severe in arterial occlusion. Vomiting was frequent. Rigidity and tenderness were more common with arterial occlusion, while distention alone was more suggestive of venous occlusion. Bleeding from the bowel occurred decidedly more frequently in the cases of venous occlusion but occurred in only fourteen cases (23 per cent) of the series; it is a valuable diagnostic sign if present. The leucocyte count was elevated to higher levels than that usually encountered in the more frequent abdominal emergencies. The rapidity of progress, the extensiveness of the disease and the tendency for progression or recurrence following operation make for poor prognosis.

MONTGOMERY.

Farks, Harry: Aneurysm of the Innominate Artery. Arch. Int. Med. 61: 898, 1938.

Three cases of aneurysm of the innominate artery are presented. All these patients had syphilis, and all died by rupture of the aneurysm. Though in early cases prompt symptomatic relief is likely to be obtained by antisyphilitic therapy, the differential diagnosis with aortic aneurysm, presenting in the neck, is important. Aortic aneurysm presents no opportunity for surgical measures, whereas aneurysm of the innominate artery has been successfully treated by surgery. None of the author's cases were treated by surgery.

MONTGOMERY.

Salatich, Peter B.: Varicose Veins of the Broad Ligament and Their Consequences. South. M. J. 31: 697, 1938.

Patients who complain of back pain, especially that relieved by resting and associated with menstrual disturbance, should be studied for possible varicose veins of the broad ligament. Diagnosis is made during pelvic examination by passing the examining fingers to the sides of the cervix, keeping in line with the axis of the uterus, pressing upward in the parametrium. If enlarged veins are present, this will cause considerable pain. Generally, the cervix is softer than normal and the body of the uterus boggy to feel. To eliminate the possibility that the ovaries or tubes are the cause of the trouble, the finger is directed

anteriorly and upward. If the tube and ovary are found not enlarged or painful, the veins are the probable cause of the trouble. The author presents a conservative operation of combined ligation of these veins and uterine suspension. He says this gives relief whereas suspension alone does not.

MONTGOMERY.

Hoenig, J.: Thromboendarteritis Obliterans Pulmonalis. Deutsches Arch. f. klin. Med. **180**: 645, 1937.

Four cases are described. In this disease the involvement starts in the smallest pulmonary arteries and spreads centrally. The histologic picture in the arteries is typical of the thromboendarteritis obliterans elsewhere. There is hypertrophy and dilatation of the right ventricle. Clinically there is circulatory failure, edema, cyanosis, and dyspnea. The lungs appear to be normal.

KATZ.

Wood, William B., and Janeway, Charles A.: Change in Plasma Volume During Recovery from Congestive Heart Failure. Arch. Int. Med. **62**: 151, 1938.

Appreciable increases in the volume of packed red blood cells, hemoglobin value, red blood cell count, and plasma protein concentration have been observed for patients during recovery from severe congestive heart failure. These changes take place rapidly, within three to six days, and are interpreted as indicating a decrease in the volume of plasma. The possible relation between the decrease in plasma volume and the disappearance of cardiac edema is discussed.

AUTHOR.

Deppe, B., and Bierhaus, H.: The Dynamics of the Human Circulation During Exercise and the Recovery Phase. Arch. f. Kreislaufforsch. **2**: 357, 1938.

During exercise on an ergometer with the subject lying horizontally, the dynamics were followed by recording simultaneously carotid and femoral pulse optically and blood pressure by auscultation. From these data the following were determined: the duration of the pulse, of systole, of diastole, and the pulse wave velocity in the aorta. The cross section area of the elastic reservoir was determined from Suter's tables. From these data the mean pressure, elastic resistance, the peripheral resistance, and the stroke volume were calculated. It was found that minute volumes, stroke volume, heart rate, elastic resistance, systolic pressure, and work of the heart were all increased during exercise. Diastolic pressure did not change and the peripheral resistance decreased. These changes are roughly proportional to the work done. The errors inherent in Broemser and Ranke's and Wezler and Böger's formulas for calculating work are compared.

KATZ.

Heymans, Corneille: The Pressoreceptive Mechanisms for the Regulation of Heart Rate, Vasomotor Tone, Blood Pressure and Blood Supply. New England J. Med. **219**: 147, 1938.

The heart rate, vasomotor tone, blood pressure, and blood supply are regulated by a number of pressoreceptive areas, the most important of which are the carotid sinus and aortic arch. Other areas provided with reflexogenic sensitivity are the left auricle and ventricle, the thoracic and mesenteric arteries, the venae cavae and right auricle and the pulmonary artery.

The role of these mechanisms of cardiovascular regulation in the mechanism of circulatory collapse and in the adaptation of blood flow and blood supply to various areas is described.

NAIDE.

Stewart, Harold J., Deitrick, John E., Crane, Norman F., and Thompson, W. P.: Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms: Observations Relating to (Part I) Rhythms Associated with Rapid Ventricular Rate and to (Part II) Rhythms Associated with Slow Ventricular Rate. J. Clin. Investigation **17:** 449, 1938.

The rapid regular and irregular rhythms in human beings at rest are associated with marked decrease in functional capacity of the heart, as measured by cardiac output per minute and per beat and the work per beat. They were associated with the dilatation of the heart. They are very inefficient rhythms, the work of the left ventricle per beat not being commensurate with the size of the heart. As a consequence, in most instances they fall outside the zone of normal circulatory function. On the other hand, rhythms associated with slow ventricular rate, such as those illustrated by complete heart block, are not incompatible with a normal circulatory function when the subject is at rest. Patients suffering from these rhythms may exhibit lowering of the basal metabolic rate as a compensatory mechanism.

AUTHOR.

Porter, William B.: Differential Diagnosis of Traumatic Aneurysm and Arteriovenous Fistula. Am. J. M. Sc. **196:** 75, 1938.

A technique is described for the positive differential diagnosis of traumatic aneurysm and arteriovenous fistula, and three illustrative cases are discussed.

The differential diagnosis in Case 1 was impossible with the use of the usual methods employed in the examination of patients with traumatic aneurysm and arteriovenous fistula. Normal venous pressure and velocity of blood flow in each arm were positive data favoring traumatic aneurysm, the diagnosis confirmed at operation.

Case 2 was most confusing. The history of local trauma, dilated regional veins, and the pulsating tumor in the popliteal space were findings common to both aneurysm and arteriovenous fistula. The aortic lesion resulting in changes in heart size, blood pressure, and pulse rate similar to those seen in arteriovenous fistula further confused the differential diagnosis. The venous pressure and velocity of blood flow were slightly lower on the side of the lesion. The difference was not significant and was accounted for by partial compression of the popliteal vein by the aneurysmal sac.

Case 3 illustrates typically the changes in venous pressure and velocity of blood flow occurring in arteriovenous fistula. The failure of compression to completely restore to normal the venous pressure and rate of blood flow is probably due to the collateral circulation around the fistulous connection. Extensive collateral circulation was demonstrated at the time of the operation, and it is felt that this technique of study may be an index to the degree of collateral blood flow and, therefore, a useful guide to the safety of surgical resection of the connecting artery and vein.

AUTHOR.

Allen, Frederick M.: The Tourniquet and Local Asphyxia. Am. J. Surg. **41:** 192, 1938.

The effects of tourniquet constriction are (1) local and (2) constitutional.

1. The local effects are due to: (a) Direct pressure damage in the zone of ligation, influenced largely by the character of the tissue and the material, form, and tightness of the ligature. Contrary to the prevailing view, the evidence indicates that narrow rubber bands or tubes are less harmful and painful than broad tourniquets.

This direct pressure injury is probably more responsible for such aftereffects as contractures and permanent paralyses than the temporary tissue asphyxia, and it is partly avoidable. (b) Local asphyxia, which can be endured for much longer periods than commonly supposed, up to fifteen hours in experimental animals, and probably for this time or even longer in man. The different viscera can withstand various shorter periods of lack of blood. These survival periods are shortened by vascular disease, infection, and especially by heat.

2. The constitutional effects represent a form of secondary shock which is of clinical and experimental importance. While the physical theory of fluid migration is well supported by facts, it appears inadequate as an etiological explanation without the assumption of a toxic factor. The experiments modify the prevalent idea of vascular permeability in shock by suggesting also a special avidity of the tissues for fluid. Likewise the special benefit of transfusions exists only within narrow limits. In general the greatest aid in shock is the injection of very abundant saline solutions beginning at the earliest possible stage.

AUTHOR.

Mackey, W. Arthur, and Scott, Lawrénce, W.: Treatment of Apoplexy by Infiltration of the Stellate Ganglion With Novocain. Brit. M. J. 2: 4043, 1938.

Ten patients in coma as the result of recent cerebrovascular accidents were treated by infiltrating the area of the stellate ganglion with a 1 per cent solution of novocain. Six of the patients had right hemiplegias and four left hemiplegias. In nineteen injections Horner's syndrome was produced fourteen times, and in nine of these immediate improvement in hemiparesis was manifest. In only one case, however, was the change dramatic. This was a young man with subacute bacterial endocarditis who, treated two hours after loss of consciousness, had immediate return of his full intellectual capacities. There was no evidence of any permanent benefit in any of the cases. Six patients died and four were dismissed from hospital with residual signs.

One patient developed respiratory paralysis immediately after the injection and required artificial respiration for one-half hour. It was believed to be due to entrance of some of the solution into a vein. No evidence of harm from the theoretically possible increased bleeding was encountered. The authors have suggested that further cases, particularly those of cerebral embolism, be studied before the method is rejected as worthless.

If improvement of cerebral function may be taken as a sign of release of spasm, the results of the procedure indicate that the cerebral vessels may react to embolic or thrombotic closure in a manner similar to that of the peripheral arteries. Although little may be added therapeutically, further treatment of apoplexy by injection of stellate ganglions and also by intravenous injections of papaverine should yield observations of value.

HINES.

Book Review

THE BIOLOGY OF ARTERIOSCLEROSIS. By M. C. Winternitz, M.D., R. M. Thomas, M.D., and P. M. LeCompte, M.D. Springfield, 1938, Charles C. Thomas, 139 pages, 116 illustrations.

The directive idea which guided these studies was the assumption that blood extravasated within the wall, especially in the intima, of the aorta and large arteries may be at least one source of the lipoidal deposit and the cause of the formation of the atheromatous plaques which characterize human simple intimal arteriosclerosis. The idea is based on the knowledge that lipoidal deposits at other sites may have their origin in extravasated blood, and the frequent observation of vascularization and hemorrhage within the lesions of human simple intimal arteriosclerosis. It is recognized by the authors that the mere demonstration of blood vessels and of extravasated blood in arteriosclerotic plaques does not constitute proof of a primary causal relationship between the former and the latter. The reverse may be true, for the vascularization and hemorrhage could be, as most students of the subject have thought, secondary to the lipoidal deposit. The authors' view has found support in their convincing demonstration by special technical methods of an "extensive vascular network" in the intima of normal blood vessels of a number of animal species other than man. The origin of the anastomosing intimal vasa has been demonstrated to be from three sources; namely, the adventitia, the region of orifices of branches, and directly from the lumen of the vessel. There are two outstanding weaknesses which must be explained before the significance of these studies can be fully recognized and the results applied to the problem of the origin of human simple arteriosclerosis. The first difficulty is that while the demonstration of anastomosing channels in the intima of normal arteries of different animal species can be accepted, yet it is a fact, which the authors fail to stress, that the arteriosclerosis which occurs in such animals is most commonly medial, characterized by degeneration and calcification of this coat and not by atheromatosis which is an important part of the lesion of human simple intimal arteriosclerosis. The second difficulty, the importance of which the authors fully recognize, is that they have failed to demonstrate anastomosing channels in the intima of normal human aorta and arteries; yet it is in this very location that simple arteriosclerosis develops in man. Until these obstacles are successfully overcome there can be no strict application of the results of this work to the complex problem of the pathogenesis of human simple arteriosclerosis. In any event, the authors have discovered many previously unknown facts about the vascularization of the walls of larger blood vessels and have developed or modified technical methods for such studies which should lead to valuable information. The book is well written; the bookmaking and reproduction of illustrations are excellent.

HARRY GOLDBLATT.

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